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RADIUM

EDITED BY

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AND

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A QUARTERLY JOURNAL DEVOTED TO THE CHEMISTRY PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES

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RADIUM

A QUARTERLY JOURNAL DEVOTED TO THE CHEMISTRY, PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES

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Edited by Charles H. Viol, Ph. D., and William H. Cameron, M. D., with the assistance of collaborators working in the fields of Radiochemistry, Radioactivity and Radiumtherapy.

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VOL. 1, New Series **JULY, 1922** **No. 2**

THE TREATMENT OF EPITHELIOMA BY RADIUM*

RUSSELL H. BOGGS, M.D., Pittsburgh, Pa.

Radium will cure a larger percentage of epitheliomas, with less destruction of tissue, leaving practically no scar or deformity, with fewer chances of a recurrence, than any other method. This is true of both basal and squamous cell epithelioma. Epithelioma or epidermoid cancer, like other types of cancer, cannot be cured unless there is entire destruction of all the cancer tissue. Of course, the method that will produce this result with the least destruction and injury to the surrounding tissues is the method of choice.

The indiscriminate use of caustics, electric coagulation, x-ray, radium or incomplete removal by surgery is to be condemned. Until lately many of the epitheliomas have been treated very inefficiently by one of the methods mentioned, but now even the patients realize that inefficient treatment will finally lead to a fatal termination.

It is astonishing how common epithelioma is and how many cases never consult a physician until the disease is so far advanced that it is incurable. Epithelioma, at least in the early stage, until lately did not seem to cause any alarm among the laity or even among the family physicians. The disease may come on so slowly that often no one takes notice of it until the lesion is far advanced. The prophylactic treatment is by far the most important and necessitates not only the education of the medical profession but also of the laity to the necessity of complete removal of all excrescences, such as warts, or degenerated moles; the removal or correction of any irritation to the skin or mucous membrane; the proper treatment of cracked lip, persistant spots of eczema and leucoplakia. Too much emphasis cannot be laid on early recognition and on the ease by which a small epithelioma can be cured by radium. Fractional or inefficient treatment by radium must not be persisted in too long even in the removal of small rodent ulcers, because

*Read before the Pittsburgh Academy of Medicine May 9, 1922.

such treatment may cause a degeneration of the healthy tissues, while a full lethal dose at the beginning would have permanently cured the lesion.

There are several types of basal cell epithelioma, but rodent ulcer is the most common. It develops from the basal cells of the Malpighian layer of the skin. It occurs on the face, neck and scalp at mucocutaneous junctions, especially about the eye, noses and ears. As a rule, it starts as a flat papule or smooth wart. It may remain a long time without any change, but resist any effort towards a cure. After a period of time it ulcerates and gradually destroys the tissues down to the bone or muscle. The base is usually covered with granulation tissue. The edges are indurated, raised and usually nodular. As the growth advances, the ulcer extends and may involve a large part of the face or scalp. The periosteum becomes invaded and vessels may be eroded and the patient may die from hemorrhage. Incomplete excision of this type

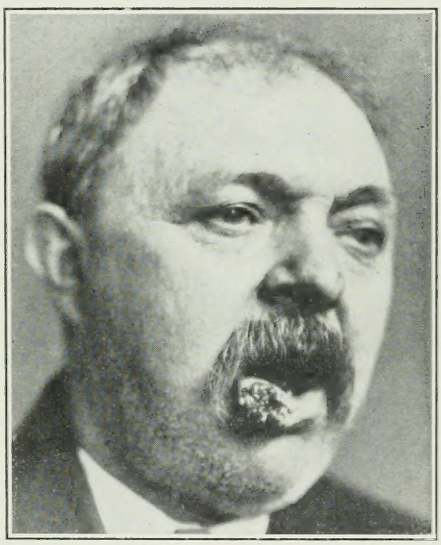

Fig. 1. Carcinoma of lip treated inadequately with x-ray by another. Patient was not further treated and has since died.

causes the growth to grow much faster. The lymphatics are seldom invaded in this type of cancer, at least not until very late. So great is the variety of structures in the epidermoid carcinoma that they must be dealt with separately in the organs in which they occur and treated accordingly.

The prognosis of both basal and squamous epithelioma varies according to the prospect of its complete removal. If the lesion is confined to the skin nearly every case can be cured. If basal epithelioma is not treated until bony structure or cartilage is involved, and if the squamous type is not treated until glandular metastases have occurred, the prognosis is grave. The size of the lesion does not always determine the prognosis. A large, slow growing epithelioma may be destroyed easily with ordinary doses of radium, while a small innocent lesion, if the glands are invaded, may resist ordinary treatment and require from

three to six times the amount of radiation it takes to complete the cure of a more extensive lesion.

Excision has almost been replaced by the use of radium in the

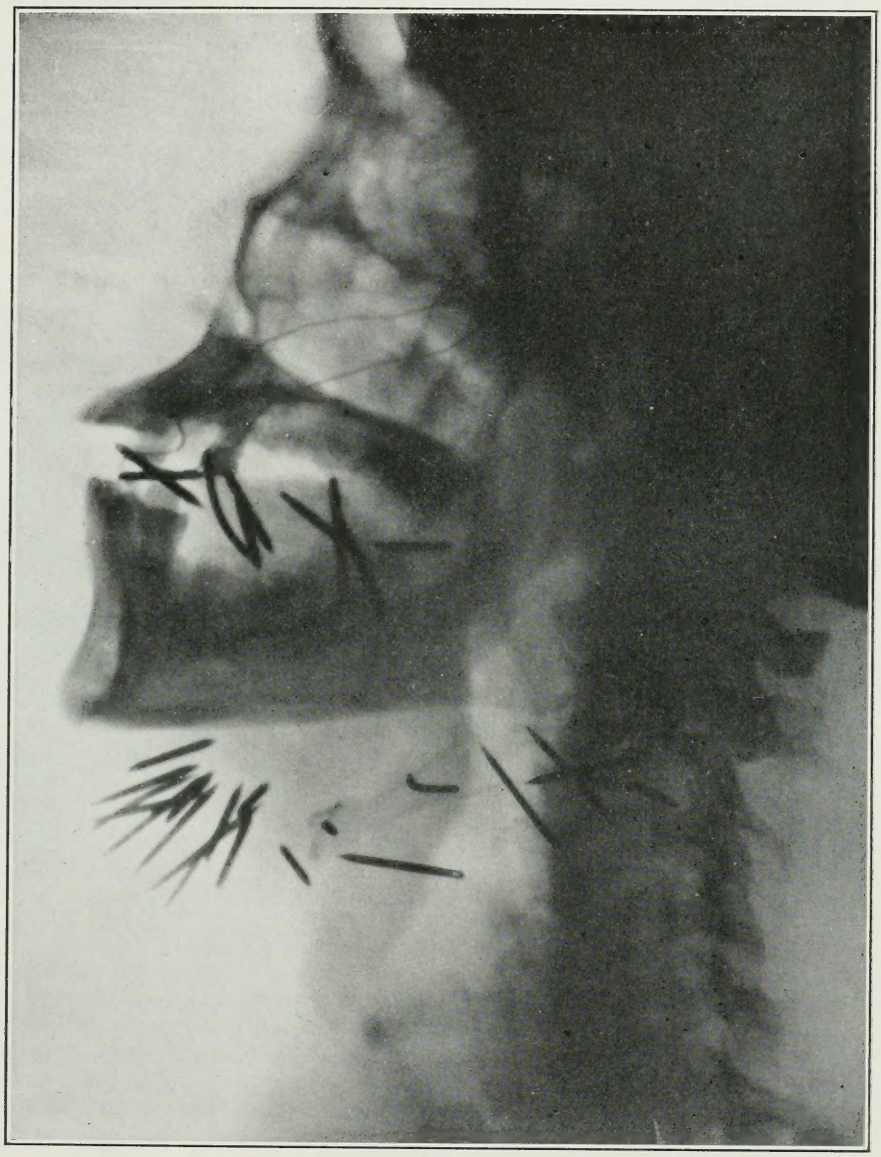

Fig. 2. X-ray photograph showing the ten milligram radium needles implanted in the tongue, submental and submaxillary glands in a case of carcinoma of the tongue. Treatment consisted in the use of the implanted needles for five hours and deep x-ray therapy on the neck.

treatment of rodent ulcer or basal cell epithelioma. It is a well known fact that if a rodent ulcer is completely excised a permanent cure will result, but end results are better by radium without leaving any scar. This is important in some locations, such as the nose, eye lid, etc., where

a surgical operation is difficult and the resultant deformity is objectionable. Large and deep seated lesions are always difficult for the surgeon to excise with all the outlying cells. One of the weaknesses in surgery is that in attempting to have a good cosmetic result there is a great possibility of leaving malignant cells. Basal cell epithelioma should always be treated early and not left until it has invaded cartilage or bone, because then it is very resistant to radiation and is almost impossible to remove surgically. Therefore, radium has been accepted by most authorities as the best method we possess today, but there are still some few who advise excision of the squamous cell epithelioma. This is because it requires more than an erythema dose to cure a lesion of this type, but in the opinion of many, the squamous cell type should be treated by radium and deep x-ray therapy because more cases can be cured, regardless of the stage of the disease.

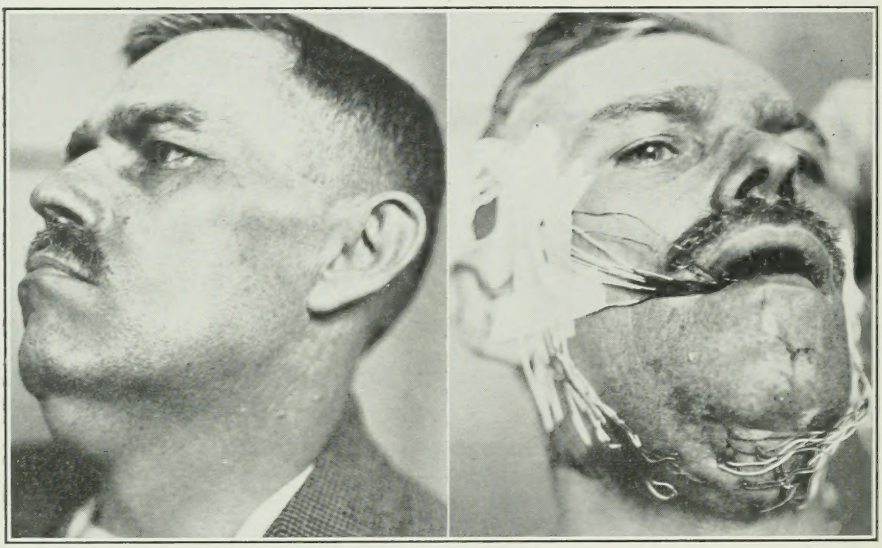

Fig. 3. Carcinoma of tongue, floor of mouth and glands (at left). Treatment consisted in the implantation as shown at right of thirty ten milligram radium needles, with some improvement.

A lethal or cancer dose in the treatment of both basal and squamous cell epithelioma must be given in order to permanently cure the lesion. An erythema dose will usually eradicate basal cell epithelioma or rodent ulcer, while it requires at least two or three times this amount in order to destroy squamous cell epithelioma.

In the past many have collected data and compiled statistics of cases of epithelioma treated by radium and the x-ray, but as most of the cases, both basal and squamous cell, were usually only given an erythema dose instead of a cancer dose, the conclusions drawn were that basal cell epithelioma could be permanently cured by radiation, while the treatment in the squamous cell type is not very successful. It is really more important to use radium in the treatment of squamous cell epithelioma than basal cell, because basal cell epithelioma can be cured in a large percentage of the cases by many other methods, such as electric coagulation or excision. The end results by excision of squamous cell epithelioma of the mouth, lip and throat, even with a

radical dissection of the glands of both sides of the neck, have proven disappointing except in the very early cases. When radium is employed, giving a lethal dose to all the cancer bearing area, employing either radium or deep x-ray therapy in conjunction with imbedding radium needles into the growth and into the lymphatic nodes which remain after surface application, it will cure more cases of squamous epithelioma of the mouth and throat, without the loss of tissue and deformity, with less inconvenience to the patient than excision. No one should attempt to treat a squamous cell epithelioma by only giving a surface erythema dose. This has accounted for the reports that epithelioma of the tongue, tonsil and buccal mucous membrane did not respond to radium, while sarcoma of the tonsil and basal epithelioma could be cured by radium and the x-ray. Unfortunately there are still many confusing an erythema

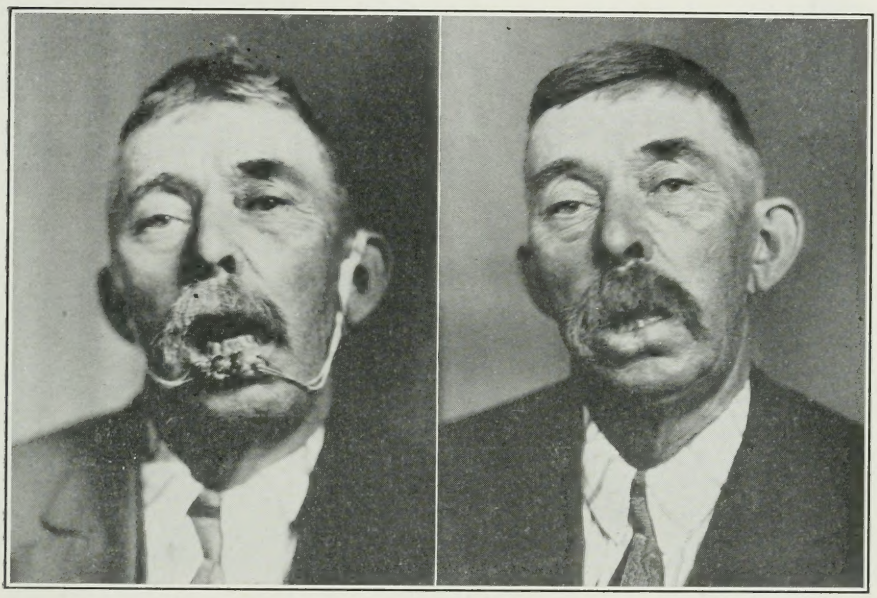

Fig. 4. Carcinoma of lip treated by implantation of four 10 milligram radium needles for two hours after previous superficial radium treatment, with x-ray treatment over glands. The result of the treatment shown at right.

with a lethal dose and many of those using radium do not realize the importance of treating the lymphatics. During the past year I have seen more than one case of squamous epithelioma of the lip which had received radium treatment and the lesion was from one-half to three-fourths healed and no treatment at all had been given to the lymphatics and in almost each case seen there were palpable lymph nodes showing that the disease had metastasized. More than an erythema dose can be given by cross-firing, using surface applications and by imbedding radium.

Primarily, I believe, every case of cancer of the lip and buccal cavity should be treated by radium locally in conjunction with deep radiation of the lymphatics of both sides of the neck. The method which seems to give the best results is surface radiation of the local growth by rather large doses of radium and thorough radiation of the lymphatics of both sides of the neck, then three or four weeks later when cell proliferation is checked imbed radium into and around the local growth.

If any palpable lymphatic nodules are present these nodules should be speared and radium imbedded.

Seventeen or eighteen years ago when we began to treat lesions of the mouth and throat by x-ray it was after the surgeon had removed as much of the local disease as was possible and in many cases a block dissection of the neck was performed. The cases referred for post-operative raying were the cases in which the center of the disease had been removed. Both the surgeon and radiologist expected radiation to destroy the remaining cancer cells. Both were disappointed because neither realized that cutting out the center of the disease never cured a patient, but hastened the cancerous process and never afforded any palliation. In fact, the patient was in a much worse condition to derive the full effect from radiotherapy than before the operation. Secondly, the

Fig. 5. Carcinoma of the lip treated by the superficial application of 75 mgm. of radium for 3 hours and deep x-ray therapy for glands of the neck. Result was a clinical cure. Note good cosmetic effect shown at right.

radiation was inefficient because a lethal dose could not be given by the crude methods used at that time. After years of treating post-operatively, no one obtaining uniform results, some radiologists advocated ante-operative radiation. In some of these cases, particularly cancer of the lower lip, the lesions responded promptly and the patient was clinically cured without operation.

Later, when we treated the local lesion with radium and the adjacent lymphatics of both sides of the neck with either deep x-ray or radium packs, the results were so much better that many considered primarily radium in the treatment of all cancers of the lip and buccal cavity. During the past three years better results have been obtained by imbedding radium in cancer of the mouth and throat. Some advocate a block dissection following radium treatment of the local growth, while the results seem to favor spearing any lymphatic enlargement and imbedding radium.

It is perfectly justifiable to treat epithelioma of the lower lip in both early and late stages, provided the proper radiation is given. The results by competent radiologists are at least equal to those of surgery in the early cases and superior after the disease has passed the local stage. It has been shown that very few cases have been cured surgically when more than one lymphatic chain is involved or when the cervical glands contain cancer cells. Broder at the Mayo-Clinic states at this stage these cases are not cured by surgery.

The type of the lesion should always be taken into consideration. Basal cell epithelioma of the lower lip begins in the skin, later involving the mucous membrane and can be cured in the early stages by almost any method, provided it is thorough, because it seldom invades the glandular system, but if it is left untreated it will progress and

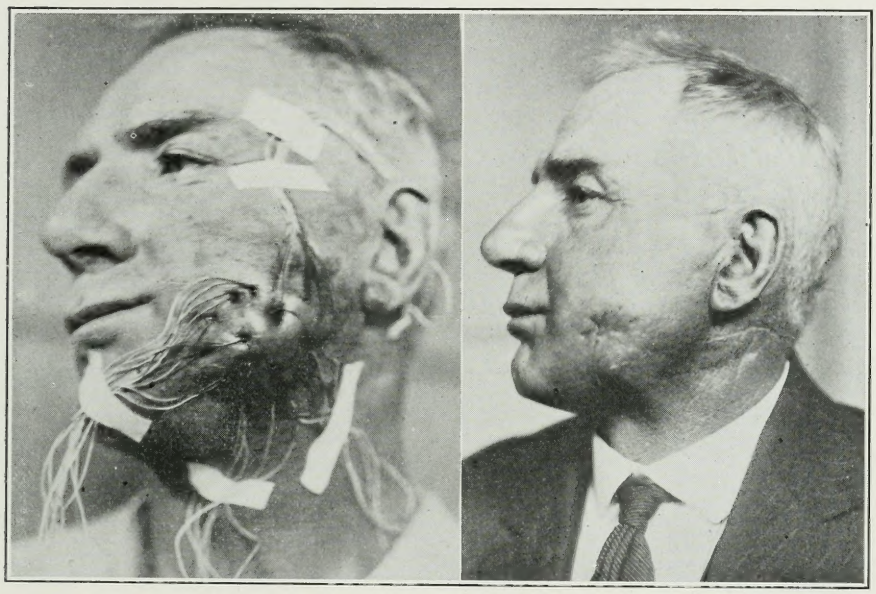

Fig. 6. Carcinoma of lower jaw checked temporarily by the implantation of 17 ten milligram radium needles for three hours, following superficial radium treatment over the growth and deep x-ray therapy applied to the glands.

finally destroy the entire lip. Squamous cell is of two varieties; superficial, which involves lymphatics later than the deep variety but destroys larger area of the mucous membrane. In the superficial type if a v-shape section is removed, it is necessary to remove a greater portion of the lower lip, the deformity producing great discomfort. This type will respond promptly to radiation but the skin below the lip and covering the chin should always be rayed, never omitting the lymphatics. The deep variety is more difficult to treat, because of the early involvement of muscle tissue and the glandular system is more prone to metastasize. If muscle tissue is invaded and destroyed to any extent, it may be advisable after the case is clinically cured to remove part of the local tissue for two reasons; first, because there may be latent cancer cells remaining in the muscle tissue and secondly, to correct the deformity caused before treatment was begun.

Treatment of cancer of the mouth and throat is very difficult and

this depends somewhat on the tissue which is involved. Epithelioma of the tongue involves the lymphatic glands the earliest and epithelioma of the mucous membrane of the cheek is most difficult to treat after it has invaded muscle tissue. The normal tissue here will not tolerate anywhere near as much radiation as the tissue of the tongue, floor of the mouth, or tonsil. These cases involving the mucous membrane of the cheek must be treated early before muscle is involved if a cure is expected by radium alone. Much more has been accomplished in cancer of the tongue than was ordinarily expected, the reason being that after surface application of radium and radiation of the lymphatics, radium can be imbedded in a large portion of the tongue and rather large doses can be given without permanent damage to normal tissue. When treating cancer of the posterior part of the tongue it is necessary to imbed

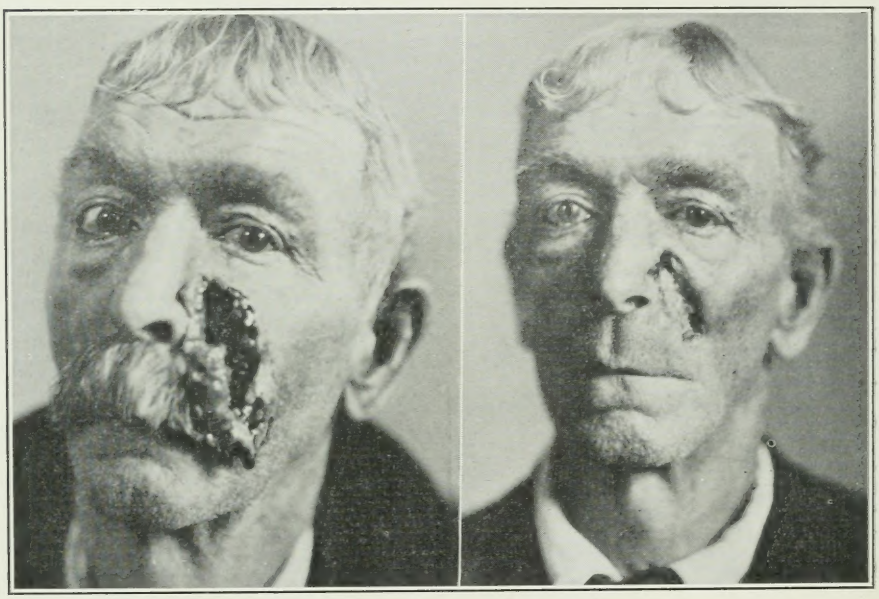

Fig. 7. Advanced epithelioma of left cheek treated by radium using total dosage of 3000 milligram hours, 1200 mgm. hrs. by pack for superficial effect and balance by pack at greater distance for deep effect. The result is a clinical cure. The patient's present condition is much better than shown at right, the site of the growth being marked by a scar.

radium into the base and also into the tissue of the tonsil of the affected side. This makes radiation quite thorough.

Cancer of the floor of the mouth gives good results when treated in the same manner. Here radium can be inserted into the growth, under the tongue and also through the skin under the chin. Cancer of the antrum has been successfully treated by opening the antrum with soldering iron as advocated by New, or by electric-coagulation and applying radium in the antrum.

Some advise curettage of nasal epithelioma before applying radium but it is usually unnecessary and in many cases has certain disadvantages. As a rule it can be performed with safety in basal cell epithelioma as there is very little danger of glandular metastases, however, removal by electro-coagulation is preferable. The recurrence of basal cell epithelioma is nearly always in the periphery and usually is seen in cases

where radium does not cover sufficient skin area to reach the outlying cells.

Basal cell epithelioma is very often resistant to radium in cases that have been inadequately treated with the rays or with other therapeutic agents. In these cases there is usually some degeneration of the tissue or there may be inflammatory tissue which contains no cancer cells but will not heal with further radiation. Sometimes, in order to kill all malignant cells in very extensive or deep growths, the massive doses of rays used may cause a fibrous degeneration in adjacent normal tissues. In all these cases excision or the use of dessication is always indicated.

The pathologist's report in a case of advanced epithelioma of the

Fig. 8. Epithelioma of the nose treated as shown at left by the implantation of five 10 milligram radium needles which were left in for three hours. The result of the treatment is shown at right.

cheek, where there had been deep ulceration which had been treated with lethal doses of radium, followed by incomplete healing with a clinical picture of epithelioma, showed presence of only scar tissue and no malignant cells when examined microscopically. This illustrates that where the cancer cells have all been killed by radiation, leaving chronic inflammatory, fibrous tissue, it is futile to persist in further radiation since this only increases the fibrous growth. Complete healing in such cases can seldom be obtained save by use of electric coagulation or free excision beyond the fibrous margin.

It is the concensus of opinion that it is unsafe to curette squamous cell epithelioma before applying radium, as there is too much danger of producing metastases. The same is true of electro-coagulation although it is recommended by some in cancer of the lip, mouth and throat preceding radium treatment. Electro-coagulation or even embedding radium should not be done until cell proliferation is checked by surface radiation. In all squamous cell epithelioma the adjacent lymphatics should

always be irradiated to the point of skin tolerance and if any palpable glands remain each should be speared and radium imbedded. After a clinical cure the site of the lesion and adjacent glands should be inspected at frequent intervals for a period of three years. Careful observation regardless of the method employed would often be the means of avoiding a destructive recurrence.

It is generally conceded that fractional doses of radium are contraindicated in the treatment of both basal and squamous cell epithelioma. It is important in all cases to estimate the physiological dose and give the maximum dose at the first treatment.

Radium, when given in full doses covering all the diseased area with the proper amount of filtration and the correct distance, will cure

Fig. 9. Epithelioma on the nose treated by implantation of two 10 milligram radium needles for four hours as shown in picture. Result was a clinical cure.

over 95 per cent. selected and between 80 and 90 per cent. of unselected cases of basal epithelioma.

With our present day technic over 90 per cent. of early cases of epithelioma of the lip can be cured. The farther advanced the disease, the smaller the ratio of cures and if there is extensive glandular involvement, the prognosis is grave. For the purpose of description, epitheliomas of the lower lip, besides the superficial and deep variety, are classified into three different stages. First, where the lesion is clinically limited to the lip, that is, there is no palpable glandular involvement; second, where there is only one chain involved, that is, the submental or the submaxillary, and third, where more than one chain of lymphatics has metastasized. In treating the first class, where there are no clinical metastases, it has been estimated that there are microscopical metastases in from 25 to 50 per cent. of the cases. Then the treatment must consist of a lethal dose to the lip, the submental and submaxillary glands. This can be best accomplished after giving as much surface application of either radium or deep x-ray therapy as the skin will

tolerate by imbedding radium into the submental and submaxillary area on both sides of the neck. This does not seem to be too radical since

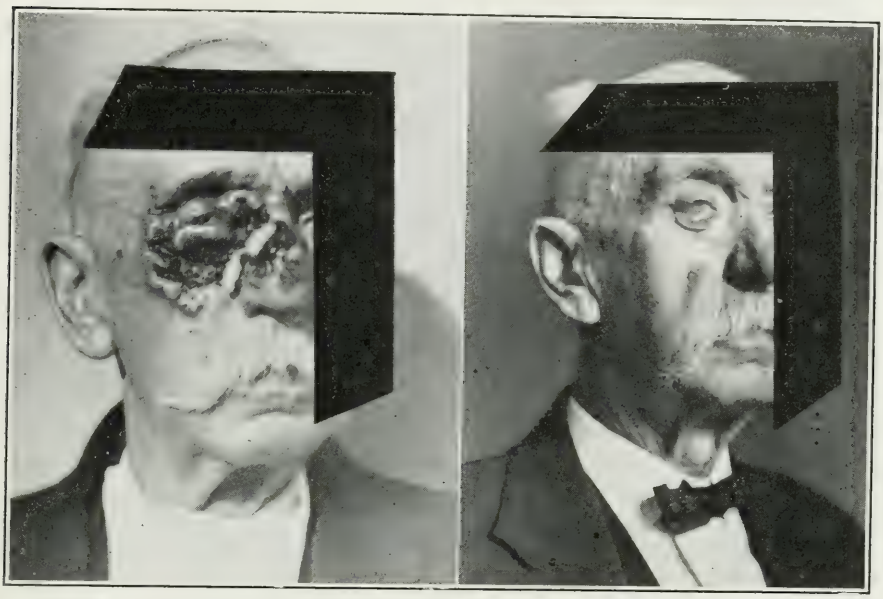

Fig. 10. Extensive epithelioma of lower eyelid, nose and cheek treated over a period of one and a half years using a total of 1800 milligram hours of radiation applied superficially. Note splendid cosmetic result as shown at right.

Fig. 11. Epithelioma above ear treated by the implantation for four hours of five 10 milligram radium needles. Result of treatment shown at right.

experience has proven that metastases occur in many cases when the treatment is given early by the ordinary methods of radiation. In my

opinion more early cases of epithelioma of the lip can be cured by radium and deep therapy when so employed than removal surgically with a block dissection of the neck. There is no reason why the radium should not be imbedded in every case of epithelioma of the lip no matter how early the case is treated.

When one chain of lymphatics is palpably enlarged, cancer cells can nearly always be found in the next chain microscopically and these patients are seldom ever cured surgically. A large percentage of these cases can be clinically cured by radiation, but naturally there will be more recurrences, this depending upon the condition of the lymphatics of the patient under treatment. Clinically it seems to be true that certain patients have a higher resistance against the spreading of carcinoma than others. This is observed in noncachectic and cachectic individuals. It has been stated that in the tissues surrounding carcinoma there is a so-called battle zone consisting histologically of advancing carcinoma cells opposed by leucocytes and connective tissue cells. This zone seems to be absent in some patients with rapid growing cancer and in patients where the resistance of normal tissue is below par.

A REPORT OF THE WORK CARRIED OUT AT THE RADIUM INSTITUTE, LONDON

From January 1st, 1921, to December 31st, 1921*

A. E. Hayward Pinch, F.R.C.S., Medical Superintendent

The Radium Institute was opened for the treatment of patients in August, 1911, so that a period of rather more than 10 years has elapsed since its inauguration. During that time some 7,750 patients have been dealt with, and nearly 100,000 treatments administered. It, therefore, seems expedient at the present juncture to attempt to review very briefly the results which have been obtained, and to indicate to the medical profession generally, the amount of benefit which may be reasonably expected from the radium treatment of various forms of disease—malignant and non-malignant.

The cases fall into four chief categories:—

(a) Those in which cure, either complete in the case of non-malignant, or apparent in the case of malignant disease may be confidently anticipated:—

Chronic eczema, seborrhœic eczema, lichenification, cavernous nævi, keloids, papillomata, keratomata, corns, rodent ulcer, lympho-sarcomata, sarcoma of the naso-pharynx.

(b) Those in which great benefit, both local and symptomatic, may be expected to ensue:—

Psoriasis, xanthelasma, xeroderma pigmentosum, Fordyce's disease, leukoplakia, capillary nævi, "port-wine" marks, spring catarrh, lupus erythematosus, lupus vulgaris, tuberculous aden-

*Reprinted by permission.

itis, vicious cicatrices, Dupuytren's contraction (early stages), exophthalmic goitre, parenchymatous goitre, splenic leucocythæmia, lymphatci leucocythæmia, lymphadenoma, mediastinal tumors, epithelioma of skin, epithelioma of cornea, epithelioma of vagina, epithelioma of urethra (female), carcinoma of breast, carcinoma of uterus, carcinoma of bladder, carcinoma of prostate, carcinoma of thyroid, sarcomata (excluding endosteal), endotheliomata, angio-neurotic œdema, arthritis deformans (early infective cases).

(c) Those in which the result is doubtful, some cases responding very well, others of like character failing to show any improvement whatsoever:—

Pruritus, neuralgia, neuritis, epithelioma of tongue, epithelioma of mouth, epithelioma of fauces, epithelioma of larynx, epithelioma of oesophagus, carcinoma of stomach, carcinoma of intestine, carcinoma of rectum, myelomata, melanomata, glycosuria.

(d) Those in which radium treatment is practically useless:—

Dupuytren's contraction (late stages), kraurosis vulvæ, adenomatous goitre, osteitis deformans, acromegaly, cysts, lipomata, enchondromata, osteomata, endosteal sarcomata, syphilis, locomotor ataxia, disseminated sclerosis, polio-myelitis, paralysis agitans.

By far the greater number of patients applying to the Radium Institute for treatment are suffering from malignant disease, and in the majority of cases the condition is far advanced and inoperable, or has already been operated upon and recurrence has taken place, and there is no possibility of further surgical intervention.

It would be quite unwarrantable to use the term "cure" when speaking of radium treatment in conditions such as the foregoing, but it may, with reason, be claimed that results have been obtained in the arrest of the progress of the disease, and in improvement of the patient's general health and comfort to a degree that cannot be excelled, and is rarely equalled by any other known medical or surgical measure. At the present moment the institute case-sheets comprise the names of many patients suffering from recurrent inoperable malignant disease who first presented themselves for treatment some seven, eight, nine or ten years ago, and who are now leading useful and comparatively healthy lives, the disease having been rendered quiescent by the treatment which they have received.

Dosage. With increasing experience it has been found possible greatly to augment the doses employed, and whereas in the early days of the institute a dose of 3,000 milligramme* hours was considered a large one, it is now quite a common event, in suitable cases, to give doses of from 20,000 to 30,000 milligramme hours, and this, if judiciously administered, occasions but very little systemic disturbance of the patient. Considerable advances have been made in the treatment of such conditions as carcinoma of the prostate, carcinoma of the bladder, carcinoma of the uterus, mediastinal tumors, splenic and lymphatic leucocythæmia, lymphadenoma, and tuberculous adenitis, and results are now frequently obtained which are far more striking than was at first anticipated.

*Important—It must be recalled that the dosage in this Report is expressed in terms of crystalline radium bromide, the radium element content of which is 53.6%. To express dosage in terms of mgm. of radium element, the unit used in the U S, it is necessary to multiply the figures given in this Report by the factor 0.536.—Ed.

The chief problem which has to be solved is the treatment with radium of deep-seated growths to which there is no adequate means of approach by way of the natural channels, but improvements in technique are being devised from time to time which are slowly but steadily lessening this difficulty. Many workers, notably in America and the Continent, are now adopting a combined method of treatment—either by diathermy followed by radium treatment, or x-ray treatment to supplement the radium radiation, and the outlook in both of these directions is distinctly hopeful, much excellent work having already been accomplished which promises a fair augury for the future.

Screening. The subject of screening has been dealt with very thoroughly, and it is now a matter of comparative simplicity so to adjust the strength of the apparatus and screening that all risk of burning a patient can be effectively eliminated. At the commencement of the work of the institute great difficulty was often experienced in dealing with patients who had been prejudiced by the statements of irresponsible and unqualified persons that radium treatment, however applied, must inevitably produce painful and persistent burns.

At the present date it is no uncommon thing for an inquiry to be made by patients or their friends as to the possible effect of a course of treatment on their blood condition and general health, but it is now clearly established that impairment of the blood is produced only by the cumulative effect of frequent and prolonged exposures to gamma radiation, and to this the patients are practically never subjected, intervals of at least six weeks being always permitted to elapse between successive treatments.

Radium and X-rays. Information is often asked for regarding the relative advantages of radium and x-rays in the treatment of disease, but the answer is by no means a simple one, and each case must be separately and carefully considered before a decision is given. X-rays, however, are generally to be preferred to radium when the condition is very wide-spread, and large areas of the body are affected—e. g., generalized psoriasis, the early stages of cancer "en cuirasse," generalized infection of the peritoneum, as met with in cases of cystic disease of the ovaries, etc. In all these conditions an enormous quantity of radium, mounted on numerous applicators, would be necessary adequately to radiate the whole affected regions at one sitting, but this can, however, be readily accomplished by means of an x-ray tube.

On the other hand, when it is desired to give an intense dose over a small area, e.g., rodent ulcer, small superficial epitheliomata, recurrent nodules after excision of the breast for carcinoma, endotheliomata of the parotid, and sarcomata in the early stages, etc., radium should be advocated, as by means of emanation applicators an extremely powerful dose can be administered to a very small area. Then, too, there are certain situations, such as the cavity of the uterus, bladder, larynx, œsophagus, stomach and rectum where it is almost impossible to give an adequate dose of x-rays, but by means of a suitable form of apparatus, radium can be quickly, safely and effectively employed in all of these situations. In the case of young children and highly nervous patients the procedure associated with x-ray treatment often proves very terrifying, and great trouble is experienced in persuading the patient to submit to the necessary manipulations. With radium this difficulty does not occur; no pain, discomfort, or annoyance is occasioned by the application, and it is a common sight to see quite young

children who are being treated for nævi or tuberculous glands, etc., playing with toys, the applicators being safely strapped in position.

The nature of the gamma radiation has not yet been satisfactorily determined, but it is considered by most physicists to be analogous to the hardest cathodal rays of an x-ray tube. Clinical experience, however, tends to show that there must be some difference between them, as quite frequently cases of lichenificaton, rodent ulcer, and lupus vulgaris are met with, which have failed to respond to x-rays, but yield promptly and satisfactorily to radium treatment.

Radium and the Brain Tissues. Anxious parents sometimes desire reassurance, when their infants are being treated for nævi of the face and scalp, that radium rays will not have any harmful effect upon the brain tissues, and this assurance may be given with every confidence. A child being treated for a cavernous nævus of the face rarely receives an exposure of more than two hours' duration at one sitting. The radiation employed in these cases is composed chiefly of medium beta rays, which possess a relatively feeble power of penetration. Several patients suffering from old rodent ulcers of many years' duration affecting the scalp have received exposures of thirty hours' duration with hard beta and gamma rays; such exposures having been repeated at intervals of two months on from six to ten occasions. In no instance has any ill effect on the patient's mental faculties, or any disturbance of the motor or sensory centers been noted. In the few cases of glioma of the brain which have received treatment, and in which the exposures have been even more intense and prolonged, the patient's general mentality does not appear to have been influenced in the slightest degree.

Diseases of Bone. It is to be noted that radium treatment is useless in all cases of disease affecting actual bone substance, whether malignant or non-malignant. It has been tried in such widely diverse conditions as rodent ulcer affecting the cranial bones, osteo-sarcoma, myositis ossificans, osteitis deformans, and ivory exostosis, and in no instance has the least benefit ever been recorded. It is now the custom at the Radium Institute when a patient suffering from rodent ulcer which has actually invaded the bony tissues applies for treatment, to recommend excision of the affected portions of the bone before any exposures are undertaken.

Cysts. With regard also to cystic conditions generally, radium treatment is of little value, more especially if the cysts be large and tense. When favorably situated, however, removal of the contents of the cyst by incision or aspiration, followed by the introduction of radium into the cyst cavity, may be utilized to induce inflammatory adhesions of the cyst walls and so prevent its reappearance.

Lipomata. Patients are occasionally sent to the institute for the treatment of lipomata. These persons are usually of the female sex, the lipomata being in exposed portions of the body, and their removal being desired for cosmetic purposes. It may be stated at once that radium has no effect whatsoever on fatty tumors, and that surgical interference alone is to be recommended to bring about the desired result.

It is to be regretted that within the past twelve months statements have been published in the lay press to the effect that radium was "a failure," and these appear to have originated in the pronouncements of some well-meaning but ill-informed practitioners concerning a subject of which they possessed but very little personal experience. As

TABLE I.

CLASSIFICATION OF CASES

DISEASE	Examined, but not treated.	Recent report not received.	Received prophylactic treatment only.	Apparently cured.	Cured.	Improved.	Not improved.	Abandoned treatment.	Dead.	Total.
Carcinoma, Squamous-celled:										
Glabrous skin	1	4	2	3	—	2	7	—	—	19
Buccal, oral, lingual, & pharyngeal mucous membrane	9	7	3	4	—	9	23	11	3	69
Oesophagus	2	—	—	—	—	3	2	—	—	7
Larynx	1	1	—	—	—	1	2	—	—	5
Vulva	—	—	2	—	—	1	1	—	—	4
Vagina	—	2	—	1	—	5	1	—	—	9
Uterus	2	18	4	1	—	38	16	4	1	84
Bladder	—	—	—	—	—	2	1	—	—	3
Cornea	—	1	—	—	—	—	—	—	—	1
Carcinoma, Spheroidal-celled:										
Breast	5	6	12	—	—	41	12	3	3	82
Thyroid	—	1	—	—	—	1	—	—	—	2
Liver	—	—	1	—	—	—	—	—	—	1
Carcinoma, Columnar-celled:										
Large intestine	2	1	1	—	—	—	2	—	1	7
Rectum	3	6	—	—	—	15	13	1	—	38
Stomach	1	—	—	—	—	2	1	—	—	4
Ovary	1	1	1	—	—	1	1	—	—	5
Prostate	—	1	—	—	—	5	—	—	—	6
Rodent ulcer	1	4	—	99	—	37	3	1	—	145
Sarcomata	2	4	4	3	—	14	8	2	3	40
Melanoma	—	—	1	—	—	1	—	—	1	3
Endothelioma	—	3	—	2	—	6	4	—	—	15
Malignant glands	1	2	—		—	1	3	1	1	9
Mediastinal tumour	—	—	2		—	1	1	1	3	8
Cerebral tumour	—	—	—		—	1	—	—	—	1
Villous tumour of bladder	—	—	—	—	—	—	1	—	—	1
Lymphadenoma	—	1	—	2	—	7	1	1	—	12
Fibroid disease of uterus	1	—	—	—	3	5	1	—	—	10
Fibromata	1	—	—	—	1	2	2	—	—	6
Naevi:										
Capillary	1	2	—	—	4	8	2	—	—	17
Cavernous	—	—	—	—	6	16	3	—	—	25
Papillomata and keratomata	—	1	—	—	30	—	1	—	—	32
Tuberculosis:										
Skin	1	—	—	—	3	6	1	—	—	11
Glands	2	—	—	—	—	5	—	—	—	7
Spring catarrh	—	—	—	—	5	4	—	—	—	9
Chronic metritis	—	—	—	—	1	3	—	—	—	4
Keloid, etc.	3	—	—	—	7	12	1	—	—	23
Lupus erythematosus	—	—	—	—	—	3	—	—	—	3
Psoriasis	—	—	—	—	—	3	—	—	—	3
Pruritus	—	—	—	—	2	2	—	—	—	4
Chronic eczema	1	—	—	—	2	3	—	—	—	6
Lichenification	—	—	—	—	2	1	—	—	—	3

TABLE I (Continued)

CLASSIFICATION OF CASES

DISEASE	Examined, but not treated.	Recent report not received.	Received prophylactic treatment only.	Apparently cured.	Cured.	Improved.	Not improved.	Abandoned treatment.	Dead.	Total.
Urticaria Pigmentosa	—	1	—	—	—	—	—	—	—	1
Leukoplakia	—	—	—	—	—	1	—	—	—	1
Lymphatic leucocythaemia	—	—	—	—	—	1	—	—	—	1
Splenic leucocythaemia	—	—	—	—	—	1	—	—	—	1
Exophthalmic goitre	1	2	—	—	—	8	1	—	—	12
Parenchymatous goitre	2	—	—	—	—	—	—	—	—	2
Dupuytren's contraction	—	—	—	—	—	2	—	—	—	2
Arthritis deformans	4	1	—	—	—	10	1	—	—	16
Chronic Prostatitis	1	—	—	—	—	—	—	—	—	1
Chronic Glossitis	1	—	—	—	—	—	—	—	—	1
Chronic Pancreatitis	—	—	—	—	—	1	—	—	—	1
Chronic Ulceration	—	—	—	—	2	1	—	—	—	3
Various	7	—	—	—	1	6	2	—	—	16
Totals	57	70	33	115	69	298	118	25	16	801

The Table of Cases refers only to those patients who were seen for the first time between 1st January, 1921, and 31st December, 1921, and does not include any cases examined prior to those dates, though many such have received treatment during 1921.

The policy of declining to treat operable cases of malignant diseases—rodent ulcer alone excepted—has been rigidly adhered to, save in those instances where the patient has positively refused to submit to operation.

The cases treated were in no instances selected, and the only ones refused were those in which the patients were practically moribund, or where the disease was of a kind for which radium therapy was manifestly unsuitable.

The column "cured" refers only to cases of a non-malignant nature, as it would be unjustifiable to claim as "cured" cases of malignant disease which have been treated for the first time during the past year.

The term "apparent cure," used in relation to cases of malignant disease, must be interpreted as representing a condition in which all trace of the original lesion or lesions has disappeared, in which there is no sign of any recurrence, and in which the patient is, so far as can be determined by a thorough and careful examination, free from any indication or symptom of the disease.

Cases have been classed under the heading "improved" only when the result of treatment has been to produce a definite and marked degree of benefit, either in the direction of retardation of the progress of the disease, diminution in the size of a growth, healing of ulceration and arrest of hæmorrhage and discharge, or of relief to such subjective symptoms as itching, tenderness, pain, dyspnœa and dysphagia

The strength of all the apparatus used in the treatment of cases is expressed in terms of hydrated radium bromide, a salt the radium element content of which is 53.6 *per cent.*

7,539 treatments were administered during the year, of which 4,075 were given free of all charge to necessitous patients.

719 emanation applicators were prepared during the year, and distributed to hospitals and medical practitioners throughout the United Kingdom for the treatment of patients.

these statements are not infrequently alluded to by patients and their friends, it is obvious that considerable harm has been done by their dissemination, and it therefore appears desirable strongly to controvert the assertion. Radium is not a failure when used intelligently and scientifically, and applied to the treatment of those conditions which experience has shown are amenable to its action. No honest worker claims, or has ever attempted to claim, that radium is to be regarded as a panacea, or as a cure for malignant disease, and many years must elapse, and much more research and clinical work be done, before it will be justifiable to use the word "cure" even in selected cases of malignant trouble. It is best, therefore, to speak only of "arrest of the disease," and this can be truthfully be affirmed in very many instances. Patients whose lives would have speedily terminated, and who would have suffered much intense agony, have been enabled by radium treatment to live for many years in comparative comfort after all the known resources of medicine and surgery had been exhausted. That in radium we possess an addition to our armamentarium of great value, is a fact which cannot be challenged, and it is distressing to think that a rash and ill-advised statement by its wide publicity should have deprived many patients of fresh hope and possible benefit.

The indiscriminate use of radium is strongly to be deprecated, especially when dealing with malignant disease. The dose, screening, and exposure employed must be most carefully considered, and the size of the tumor, the presence or absence of definite lymphatic infection, the existence of metastatic deposits, and the exact pathological nature of the growth, determined. The last factor is of great importance, as the radium rays exhibit very definite variations in their effect upon the different types of pathological neoplasms, sarcomatous being much more vulnerable than epitheliomatous cells. Further, the dosage needs to be very accurately adjusted to the size of the mass treated. The "law of the inverse square" must constantly be kept in mind, as if the center only of a very large growth be treated by the burying of a radium tube within its substance, the destructive or degenerative action of the radium ceases at a distance of a few centimetres from the tube, and the cells at the periphery of the growth are influenced only by a weak stimulant action of the rays, which may quite possibly induce a rapid growth of the distant portions of the tumor. In such cases, therefore, both central and peripheral radiation of a powerful type should be employed if any measure of success is to result. It is the invariable practice at the Radium Institute when treating cases of cancer of the breast, cancer of the uterus, etc., to radiate as thoroughly as possible the lymphatics leading from the affected area for some considerable distance around it, and in this fashion permeation of the lymph channels by carcinomatous cells is greatly retarded, or entirely prevented.

The question is sometimes raised whether the radium radiation of a primary growth may not possibly produce a rapid and general dissemination of the malignant cells—in much the same way as was sometimes seen in the early days of tuberculin treatment when an overdose of the tuberculin injection was followed by the appearance of an acute miliary tuberculosis. A few cases suggestive of this possibility have been recorded by competent observers, but investigation has failed to reveal any very definite reason for attributing the carcinomatosis to the radium reaction, rather than to a rapid enfeeblement of the patient's

general power of resistance from some other associated condition. On the other hand, there is some evidence which would warrant the inference that in certain cases the absorption by the blood stream and lymphatics of the cells which have been destroyed by the radium acts as an autogenous vaccine, and that this strongly reinforces the patient's specific resistance to the disease.

Radium Emanation. The employment of radium emanation as a therapeutic agent is steadily increasing, and its field of usefulness broadens from day to day, as its merits and advantages become more widely recognized. The manipulation of the emanation is a highly technical process, and necessitates the attention and services of a staff of specially trained physicists, whose measurements of its initial radio-activity, and its subsequent variations can be relied upon absolutely. There is further the fact that the emanation can only be obtained from solutions of radium salts; the quantity is limited, and bears a strict ratio to the amount of the parent salt. A gramme of radium bromide in solution will furnish a daily output of radium emanation possessing a radio-activity equivalent to that of 150 mgrs. of radium bromide. This emanation slowly decays, its initial radio-activity being reduced to one-half in 3.85 days, and to one-fifth in 8.8 days. During the first twenty-four hours the loss is exactly 16 per cent. (2 per cent. every three hours). This rate of decay never varies, and it is thus a perfectly simple matter to prepare an apparatus the mean activity of which during a period of twenty-four hours would be exactly equivalent to that of a radium salt apparatus of a stated strength.

As the present market price of radium bromide is about 15,000 pounds sterling a gramme, and at least, two grammes are necessary for the production of emanation in sufficient amount to treat even a modest number of patients daily, it is obvious that the handling of radium emanation in a really adequate manner can only be undertaken at hospitals or institutes which are in a position to incur a very large capital charge in acquiring the requisite amount of radium salt; and on this account, unless the price of radium falls very considerably, it appears highly probable that emanation work will for a long time be limited almost exclusively to those institutions which already have a large amount of radium, and a specially trained staff. The Radium Institute is fortunate in possessing both these requirements, and its facilities for radium emanation work, both physical and clinical, are unrivalled in this country.

Radium emanation may be employed for therapeutic purposes in three ways:—

1. *By inhalation.*—This method obtained a great vogue on the Continent in the years immediately preceding the war. Most of the spas and bathing establishments were provided with radium emanatoria, luxuriously equipped buildings containing rooms the air of which was refreshed from time to time with small quantities of radium emanation and oxygen, or radium emanation only.

The patients undergoing the treatment were immured in these rooms for periods of three, four or more hours daily, during which time they breathed the emanation charged air. This method of treatment made slight headway in the British Isles, and it now appears to be but little favored on the Continent.

Extravagant claims were made as to its therapeutic value in the treatment of widely differing forms of disease, but these have been only

poorly substantiated by subsequent clinical observation, and it is an open question whether the greater proportion of the cures, announced were not due as much to the power of suggestion as to the physical effects of the radium emanation.

2. *By ingestion.*—Radium emanation is dissolved in water, and administered to patients daily for periods of six, nine, or twelve weeks or longer. The strength of the solution furnished by the Radium Institute is two millicuries per litre, and of this, patients take 250 c.c. during each twenty-four hours.

The principal conditions benefited by this form of treatment are arthritis deformans, glycosuria, arterio-sclerosis, and the extremely rare malady angio-neurotic œdema.

Not all cases of arthritis deformans are amenable to radium emanation. The patients most favorably influenced are those in whom fibrous, as distinct from osseous changes, are predominant, and the condition infective rather than traumatic in origin. Cases of long standing, with bony ankylosis, osteophytic formation, or ulceration of articular cartilages, derive but little benefit beyond possible relief from pain. Patients suffering from glycosuria or arterio-sclerosis sometimes improve very greatly after a prolonged course of treatment with radium emanation solution, but they should be warned that the improvement will probably be very gradual.

Angio-neurotic œdema responds in a most striking manner. The disease is but seldom met with, but when it does occur is apt to prove very resistant to general medical treatment, and to recur with distressing frequency. In the few cases that have been treated by the drinking of radium emanation solution the result has been most gratifying. The condition has speedily cleared up, and the patients have remained free from their trouble for a very long time, or have been completely rid of it.

3. *By inclusion.*—In glass or metal tubes and containers, and used for the radiation of diseased tissues in precisely the same fashion as radium salt apparatus.

The idea is prevalent in some quarters that radium emanation apparatus is less effective than radium salt apparatus, but it cannot be too strongly emphasized that their therapeutical properties are indentical. In addition, radium emanation possesses certain special advantages. Being a gas it is both compressible and expansile, and these qualities are peculiarly valuable in the making of applicators, it being possible to concentrate the radio-activity very greatly, and to prepare a tube of equal activity to any given radium salt tube, but only one-twentieth of its size. This is of great use in the treatment of small malignant growths or tiny nodules of recurrence, enabling an intensely powerful radiation to be given in a very small area. Conversely, if it is desired to give a weak radiation over a large area a suitable metal emanation container can be made, and charged with the necessary amount of gas to give the precise degree of weak radiation required.

Further, the emanation possesses no intrinsic value, and should an emanation applicator be mislaid or destroyed, the only pecuniary loss incurred is the value of the metal container. This permits radium emanation tubes and applicators to be sent on hire or loan to all parts of the United Kingdom; no security or insurance being demanded as would be the case if radium salt apparatus were despatched.

Advice is freely given to medical practitioners in the treatment of disease with radium emanation apparatus, and if precise information

is furnished as to the nature and extent of the disease or growth, a suitable apparatus with full instructions as to technique can usually be forwarded to any address in the British Isles within two or three days.

RADIUM THERAPY IN DISEASES OF WOMEN

Apparatus. The amount of radium bromide,* or its equivalent in some other radium salt, requisite for the satisfactory treatment of gynæcological disorders should be at the very least five hundred milligrammes, which should be utilized to prepare:—

1 tube of 100 mgrs.	—	100
2 tubes of 50 mgrs. each	—	100
4 tubes of 25 mgrs. each	—	100
2 rectangular flat varnished applicators, 3 by 2 centimetres "full strength," each containing 60 mgrs.	—	120
2 rectangular flat varnished applicators, 3 by 2 centimetres, "half strength," each containing 30 mgrs.	—	60
1 square flat varnished applicator, 1.5 by 1.5 centimetre	—	20
Total		500 mgrs.

Radium emanation apparatus of the same shape, size and activity may be used instead of radium salt apparatus, when an adequate supply of emanation is available.

The set of screens should comprise:—

(1) Screens of 1 mm. silver and 2 mm. lead for the 100 mgrs. and 50 mgrs. tubes.

(2) Screens of 1 mm. silver and 0.3 mm. platinum for the 25 mgrs. tubes.

The screens for the 50 and 25 mgrs. tubes should have the closed end pointed, to facilitate their insertion into small growths and recurrent nodules.

The open end of the screens should be fitted with a screw thread to permit of the attachment of an eyeletted stopper with a silk thread; or a pliable silver wire eyelet, as occasion demands.

(3) Screens of 0.01 mm. aluminum; 1 mm. silver; 0.1 mm. and 2 mm. lead, accurately shaped to fit the surface of the different flat varnished applicators.

Technique. No instruments other than those generally employed in gynæcological work are necessary, though it will be found an advantage to have all specula of the Fergusson type fitted with conical obturators. In cases of carcinoma of long standing the vaginal walls are often so infiltrated that the passage of a cylindrical speculum with abrupt edges is difficult, and occasions the patient considerable pain. The use of an obturator prevents this occurrence. When the introitus vaginæ is contracted and rigid, barely permitting the insertion of the forefinger, the smallest-sized proctoscope, such as used for children, will be found very useful. Its passage causes but little discomfort, and it effectively illuminates the cervix, fornices, etc.

The dorsal position is the most satisfactory one for the routine examination of the patient and it usually suffices for treatment also, though in some cases the lithotomy position is essential. When introducing radium tubes into the uterine cavity, cervical canal, substance of the cervix, broad ligaments, urethra or bladder all reasonable aseptic and antiseptic precautions should be observed, and the operator should wear rubber gloves to minimize the risk of infection.

The use of a tampon or light gauze packing generally suffices to keep the radium tubes in position when inserted into vagina, uterus,

*See note on page 125.

or broad ligaments, a silken thread being passed through the eyeletted stopper of the tube screen, brought out of the vagina, and fastened to the buttocks with strapping. Traction on the thread when the exposure is completed easily removes the tube. In dealing with intra-urethral or intra-vesical growths, a pliable silver wire is attached to one end of the tube screen which can be so bent as to maintain the tube in any position desired.

The passage of radium rays through thick screens of heavy metal gives rise to the production of "secondary rays," which often exercise a very irritating effect upon the normal skin and mucous membranes. Their absorption is, therefore, a matter of considerable importance. When using the flat applicators with metal screens the absorption of these secondary rays may be effected by the interposition of many pieces of black paper, with lint and thin rubber sheeting over all, between the outer surfaces of the metal screen and the skin of the patient. Or the same result may be obtained by covering all the thick metal screens with a layer of aluminum 0.2 mm. in thickness. The aluminum sheathing absorbs all the secondary rays from the heavier metals, and emits only a few non-irritant ones itself.

When using tube apparatus the metal screen is covered, as a matter of routine, with rubber tubing 3 mm. in thickness, which will effectively absorb the secondary radiation. This precaution is very necessary in intravaginal applications, as the secondary rays, if unabsorbed, are capable of exciting a severe vaginitis and proctitis. It is also advisable when treating disease affecting the anterior vaginal wall only, to protect the posterior wall by a liberal packing of gauze between it and the apparatus. In intra-uterine or intracervical applications for malignant disease, when but little if any normal mucosa remains; or when actually embedding tubes in the primary growth, recurrent nodules, or infiltrated areas, the action of the secondary rays may be disregarded, and the metal tube screens used without the addition of rubber sheathing.

Patients who have received an intra-vaginal radium treatment should be instructed to use some simple non-irritating vaginal douche daily for about four weeks after the exposure, as this will prevent the occurrence of an adhesive vaginitis, which is sometimes seen in very susceptible subjects.

THE TREATMENT OF DISEASES OF WOMEN BY RADIUM

A.—DISEASES OF THE VULVA

1. *Lichenification.* This condition is usually found affecting the labia majora or mons veneris, and is generally accompanied by an almost intolerable pruritus. In many cases radium will effect a great improvement, the itching rapidly subsiding, and the skin becoming normal in appearance.

A "half strength" applicator screened with 0.01 mm. of aluminum is used, and an exposure of from ten to twenty minutes' duration—varying with the state of the lesion—given. The exposure may have to be repeated at intervals of three weeks for some months.

In a few cases a permanent cure is obtained, but usually the condition reappears after an interval of a year or longer.

2. *Leukoplakia.* This condition in its earlier stages is often speedily cleared up by radium treatment, though it has a great tendency to recurrence.

The screening and duration of the exposures have to be modified according to the stage of the disease. When the opacity and whiteness are not very pronounced, and there is but little if any plaque formation, "half strength" applicators screened with 0.1 mm. of lead should be used, and an exposure of one and a half to three hours' duration given. In the later stages, when definite placques are present with fissuring and commencing ulceration, screening of 1 mm. of silver should be adopted, and the exposure lengthened to twelve, fifteen or eighteen hours, according to the condition. Exfoliation of the thickened patches usually occurs in three or four weeks' time, leaving smooth hyperæmic areas. This congestion gradually subsides, and the skin may become normal, and remain so, though more commonly the condition recurs after about six months.

3. *Kraurosis Vulvae.* The etiology of this disease is obscure, but there is some evidence which supports the view that it is associated with a loss of the internal secretion of the ovaries. It is most generally met with in women who have passed the menopause, or on whom oophorectomy has been performed.

The pathological changes are those of a progressive atrophy of the epidermis and dense fibrous infiltration of the corium. In the very few cases which have been treated in the Radium Institute no benefit has been noted.

4. *Papillomata.* These lesions, whether of simple or gonorrhœal origin, yield readily to radium treatment. An exposure of one hour or one hour and a half's duration to a "full strength" applicator, unscreened, produces disintegration or exfoliation of the growths in four or five weeks' time.

As these lesions are very strongly auto-infective, it is important to treat the whole affected region at the same time, so that no focus of fresh infection shall be left when the reaction has terminated.

5. *Rodent Ulcer.* This condition is very rarely met with on the vulva, but when it does occur, is found affecting the outer surface of the labia majora, and has often existed for some considerable time before its true character has been recognized. It makes its appearance as a smooth flattened nodule, often with an umbilicated center, which at a later stage ulcerates, leaving a raw depressed base with hard rolled edges. One exposure with a "full strength" applicator, unscreened, of from one and a half to two hours' duration may be relied upon to produce a cure.

6. *Epithelioma.* This may be primary in its origin, but more frequently is found as a sequela of chronic leukoplakia. The inner surface of the labia majora or the clitoris are the most common sites for its occurrence.

It is an unfortunate fact that patients suffering from epithelioma of the vulva rarely apply for treatment until the condition is far advanced, and quite inoperable. Whenever the growth is found to be operable, prompt and free excision, with removal of the inguinal glands, is recommended, but if the patient declines operation, or the condition is too far advanced for surgical intervention, radium treatment is given.

If the lesion be small, circumscribed, and with but little subjacent induration, an intensive destructive reaction is produced by the burying of a 25 mgrs. tube, screened with 0.3 mm. of platinum in its substance for twelve hours, and the external use of a "full strength" applicator

unscreened applied to the surface of the growth for one and a half to two hours. The reaction produced by these measures is severe, and a depressed scar is left, but the result is usually satisfactory.

Extensive flattened growths with commencing subjacent infiltration—pavement epitheliomata—are best treated with "half strength" applicators screened with 0.1 mm. of lead, and applied to the surface of the lesion on three successive days for three, four or five hours each day, according to its thickness. The series of exposures will have to be repeated at intervals of about six weeks. In favorable cases gradual disintegration and exfoliation of the thickened ulcerated surfaces, with lessening of the infiltration, takes place, and the progress of the disease is arrested.

In very advanced cases, with deep ulceration, infiltration of the underlying tissues, and definite infection of the inguinal lymphatics, prolonged exposures of twenty to thirty hours' duration with "full strength" applicators screened with 2 mm. of lead should be given. Such treatment may serve to heal or lessen the ulceration, diminish the infiltration, ameliorate the pain, and retard the progress of the disease, but it cannot do more.

7. *Sarcoma.* Sarcoma of the vulva is but rarely met with. It usually appears as a rounded swelling in the substance of a labium majus and may at first be mistaken for a fibroma. It grows rapidly by reason of the great vascularity of the parts, and ulceration and hæmorrhage quickly supervene. Operation, if practicable, should be undertaken at the earliest possible moment, but if this cannot be done radium treatment may be tried. One or more tubes containing 100 to 150 mgrs. screened with 1 mm. of silver, should be embedded in the growth, and "full strength" applicators screened with 2 mm. of lead applied to the periphery of the tumor. The exposures should be of twenty-four hours' duration and repeated after an interval of six weeks if necessary. The prognosis in these cases is always very grave.

B.—DISEASES OF THE VAGINA

1. *Cysts.* (*Mucous, Gartnerian, Peri-urethral*). Radium is of but little use in the treatment of any kind of vaginal cyst, and their removal by surgical means should always be recommended. In those cases where this procedure has been negatived for any reason, incision of the cyst and evacuation of its contents may be followed by the introduction of a tube 50 to 100 mgrs., screened with 1 mm. of silver, into the cavity for twenty-four hours. This will excite an inflammatory reaction, followed by an adhesive fibrosis of the cyst walls.

2. *Polypi.* These growths prove very amenable to radium treatment. A 100 mgr. tube screened with 2 mm. of lead and rubber to absorb the secondary rays, which might prove irritating to the normal vaginal mucosa, is placed in contact with the affected area, and maintained in the desired position by light gauze packing. An exposure of twenty-four to thirty hours' duration is given, and repeated if necessary at intervals of six weeks. Hæmorrhage is speedily arrested, the polypi steadily shrink, and ultimately disappear, leaving a healthy mucosa. There is but little probability of recurrence.

3. *Carcinoma.* This may be:—

(a) Primary —squamous epithelioma; or

(b) Secondary:—

(1) To carcinoma of cervix—squamous celled.
(2) To carcinoma of body of uterus or rectum—columnar celled.

(a) Primary carcinoma of the vagina is but seldom met with in young women, and generally occurs some time after the establishment of the menopause. It commonly affects the posterior vaginal wall, commencing as a hard raised nodule, which speedily ulcerates, and gradually infiltrates the vaginal walls. In these cases the patients' age and general condition frequently negative operation, so that radium treatment is adopted. The immediate result is very often encouraging, the ulceration is healed, and the growth greatly diminished in size, sometimes it completely disappears, leaving only an indurated area at its site. Recurrence is, however, extremely probable, and on this account the patients must be regularly examined at frequent intervals, so that any recrudescence may be dealt with promptly.

The routine treatment consists of twenty-four hours' exposure with a tube or "full strength" applicator—according to the shape, and size of the lesion—screened with 2 mm. of lead, and placed in accurate apposition with the growth.

(b) Secondary.—Squamous celled by extension from cervix, and columnar celled by extension from rectum, or by metastases from the body of the uterus. These growths should be treated in precisely the same fashion as the primary carcinoma of the vagina, but the prognosis is not so good by reason of the existence of a primary growth elsewhere, and its effect upon the patient's general condition.

It is worthy of note that metastatic deposits—columnar celled, from carcinoma of the uterine body—occurring in the vaginal wall are extremely susceptible to radium. They rapidly disappear under the treatment above indicated, and very rarely recur.

4. *Sarcoma.* Primary sarcoma of the vagina is even more rare than primary carcinoma, and no case of the primary sarcoma of childhood—sarcoma botyroides—has been treated at the institute.

In two cases of primary sarcoma occurring in adult women some temporary improvement was effected by the use of tubes of 100 mgrs., screened with 1 mm. of silver, and buried within the growth; supplemented by external radiation with "full strength" applicators screened with 2 mm. of lead. Both cases were quite inoperable when first seen, and progressed to a fatal termination.

C.—DISEASES OF THE UTERUS

1. *Endocervicitis* (*Cervical endometritis*). Chronic cases of this condition which have proved refractory to all routine methods of treatment are often very favorably influenced by radium, more especially when there is no antecedent history of gonorrhœal or other acute pyogenic infection. It is advisable to limit the treatment to the cervical canal and surface of the cervix, and to avoid trespassing beyond the internal os. For this purpose the use of a special mushroom-shaped applicator devised by the late Dr. Louis Wickham is to be recommended. The stem is 2 centimetres in length, and the diameter of the mushroom-like top 2 centimetres, and the apparatus is of the "full strength" type. Screening of 1 mm. of silver is employed, and two exposures, each of six hours' duration, are given on successive days. The series of exposures is repeated after a period of five or six weeks. The treatment induces a gradual healing of the raw abraded surface, which becomes

covered with healthy epithelium, the discharge is arrested, and the general feeling of discomfort abolished.

2. *Chronic Metritis. Uterine Fibrosis. Subinvolution.*—Patients suffering from any of these conditions have much in common. The uterus is symmetrically enlarged, the patient has menorrhagia or metrorrhagia, with possibly some associated leucorrhea, and complains of a chronic sacral and iliac pain. These cases often prove most intractable, the excessive hæmorrhage and almost incessant pain weakening the patient, causing her to become depressed, self-centered and neurotic, a trial to her friends, and a problem to her medical advisers.

Treatment by drugs alone rarely proves effective, and the cases sooner or later fall into the surgeon's hands. Curetting, amputation of the cervix, excision of a portion of the body of the uterus, and, as a final resource, hysterectomy may be performed. Many patients are strongly averse to operative interference, and here radium treatment is of great value, rapidly improving the patient's condition, and if proceeded with, going on to complete cure. A tube of 100 to 150 mgrs., screened with 2 mm. of lead and rubber should be introduced into the uterine cavity, and flat applicators containing 100 to 160 mgrs., screened in similar fashion, placed over the fundus uteri just above the pubes. The exposure in each situation should be twenty-four hours.

In very susceptible patients one such treatment may serve to bring about a cure, but generally two or three treatments at intervals of three months are necessary. If the treatment has to be repeated two or three times the patient must be warned of the possibility of prematurely inducing the menopause. The congestive reaction attendant upon the radium reaction not infrequently causes the first period after the exposures to be even more profuse than before, but with successive periods the amount lost gradually diminishes, until the flow returns to normal, or amenorrhæa occurs.

3. *Uterine Fibroids.* Some judgment should be exercised in the selection of cases of fibromyomata of the uterus for treatment by radium. The existing signs and symptoms must be carefully considered, the size of the growth, its position, subserous, interstitial, or submucous, ascertained; the presence or absence of pressure symptoms, and of menorrhagia or metrorrhagia noted. The cases which are most likely to be benefited are those in which the growth is more myomatous than fibromatous in character, moderate in size, and not the subject of inflammatory or degenerative changes. The treatment is identical with that above indicated for chronic metritis, and the same caution as to the possible premature induction of the menopause should be observed.

4. *Carcinoma of the Uterus.*

(1) *Carcinoma of the Cervix.*—When dealing with a case of carcinoma of the cervix a clear opinion should first be formed as to the operability or otherwise of the growth, and cases should be grouped into three main classes:—

(a) Operable cases.

(b) Border-line cases.

(c) Inoperable cases.

In the first group the correct treatment should be operation, followed by a thorough course of radium irradiation.

In the second group the procedure should be radiation followed by operation, provided the result of the treatment has been sufficiently definite to warrant attempts at surgical interference.

In the third group radiation should be relied upon principally, but it may advantageously be supplemented by such local operations as removal of fungating portions of the growth by excision, scraping, or diathermy.

Many workers are now advocating the radium treatment of early operable cases of carcinoma of the cervix by radiation alone, and the figures which they advance in support of their claim cannot be disregarded. At present, however, it would appear premature blindly to follow their lead, and early performance of Wertheim's hysterectomy in skilled hands, followed by a thorough course of radiation, still appears to be the line of action which is most likely to free the patient entirely from her trouble.

The local and symptomatic effects of radium treatment in carcinoma of the cervix are usually very striking, and the benefit obtained not infrequently imbues the patient with a false sense of security; the symptoms which caused her so much pain and discomfort having disappeared, she imagines the disease to have been eradicated completely, and ceases to attend for examination and treatment until, after a lapse of some time, fresh symptoms make their development; and when the patient is next examined the disease is found to have affected parts beyond the effective range of radium. For this reason it is imperative that all patients receiving radium treatment for carcinoma of the uterus be instructed to report at intervals not exceeding three months for a very long period of time.

General irradiation with powerful applicators applied in the iliac fossa, and immediately above the pubes, will do much to retard dissemination by the lymphatics. The routes taken by the permeating cells are well known, and the progress is comparatively slow, and so long as it is confined to the superficial lymphatics of the uterus and the parametrium, external irradiation will prove fairly effective. When, however, the disease has reached the iliac glands, the depth at which these structures are situate from the vaginal cavity and abdominal wall is such as seriously to militate against the effective action of radium irradiation.

A method has recently been devised by Dr. Franz Daels, of Belgium, who has succeeded in developing a special technique which permits the retro-peritoneal application of screened radium tubes in actual contact with the surface of the infected glands. The procedure is still under trial, but the results hitherto obtained are distinctly encouraging.

From a clinical standpoint, carcinoma of the cervix presents three well-marked varieties:—

(1) The endocervical or medullary type.
(2) The flattened ulcerated type.
(3) The proliferative fungating type.

Each variety requires a somewhat different method of treatment.

(1) *The Endocervical or Medullary Type.*—These tumors originate in the mucosa of the cervical canal and form circumscribed nodular growths, unaccompanied by any external ulceration: the predominant early symptoms are an occasional slight uterine hæmorrhage and a scanty vaginal discharge. Vaginal examination reveals little more than an enlarged and somewhat nodular indurated cervix. These growths sooner

or later break down, ulceration and disintegration rapidly occur, and the cervix is speedily transformed into a crateriform ulcer, with its apex at the internal os; its walls are thin, hard, and extremely friable. This is by far the most malignant type of the disease; lymphatic infection takes place at an early date, and involvement of the base of the bladder, leading to the formation of a vesico-vaginal fistula, is commonly observed.

In this type of growth a tube of 100 to 150 mgrs., screened with 1 mm. of silver, should be inserted within the cervical canal for twenty-four hours. This should be supplemented with one or more tubes of 25 mgrs., screened with 0.3 mm. of platinum, and inserted into the thickened cervical walls, or into the nodular infiltrations in that situation. The exposures here should be of twelve hours' duration. If definite infiltration of either or both of the broad ligaments be present, a radium tube, or tubes of 50 mgrs. activity, screened with 1 mm. of silver, should be inserted into the infiltrated area, an exposure of twenty-four hours' duration being given there.

In addition to the foregoing a general irradiation of the pelvic cavity should be carried out by means of flat applicators containing 150 to 200 mgrs., screened with 2 mm. of lead and applied immediately above the pubes, and in each iliac fossa. The exposure here should be from twenty-four to thirty hours' duration, and it is advisable slightly to move the position of the applicators from time to time, in order to avoid the possibility of producing skin vesication. The exposure may be repeated after an interval of six weeks, but not earlier.

(2) *The Flattened Ulcerated Type.*—In these cases the disease manifests itself as a flattened superficial ulcer with a hard edge and a flat granular base. It much resembles a simple erosion, and is not infrequently mistaken for the same. This growth infiltrates but slowly, and tends to spread rather by a surface extension.

Treatment in these cases is best carried out by means of the small 25 mgrs. tubes screened with 1 mm. of silver, and the most satisfactory way of doing this is to take a mould of the diseased cervix with dental modelling compound. When this is withdrawn, the tubes are embedded in grooves on that portion of the mould which will come in contact with the surface of the ulcer, and the mould carrying the tubes is re-inserted, and maintained in accurate position by gauze packing. The exposure should be of twenty-four hours' duration, and may be repeated after the expiry of six weeks. The same procedure with regard to the external irradiation of the pelvic cavity as indicated in the previous case should be carried out.

(3) *The Proliferative Fungating Type.*—This class is characterized by the so-called "cauliflower" growth which springs from the surface of the cervix, forming an irregular fungating friable mass which may almost completely fill the vaginal cavity. Here it is advisable before proceeding to radium treatment to remove as much of the growth as possible by excision, curetting, cautery, or diathermy.

The remains of the cervix should then be treated by the insertion of a 100 tube, screened with 1 mm. of silver, into the cervical canal for twenty-four hours, and any outlying nodules that may have escaped the surgical procedures should be treated by the insertion of a 25-mgrs. tube, screened with 0.3 mm. of platinum, into their substance for twelve hours. Here, too, a general radiation of the pelvic cavity should be

adopted as a matter of routine, and the exposures repeated at an interval of six weeks if necessary.

The local and symptomatic benefit which usually follows the procedures above indicated is usually most striking; hæmorrhage and discharge are arrested, ulceration is healed, the growth is diminished, the parametric infiltration is reduced, and pain ameliorated. In the "border-line" cases some patients respond in such excellent fashion that within three or four weeks of the exposure the surgeon is inclined to regard as quite operable a case which before he was strongly averse to interfering with. In these cases the reduction of the infiltration, and the lessening of the accompanying fixation are often most pronounced. This is possibly due to the fact that the peri-uterine infiltration is of a composite character, both carcinomatous and inflammatory, and the action of the radium has done much towards lessening the inflammatory effusion. It is, however, important in these "border-line" cases that too long a period of time should not be permitted to elapse between the radium treatment and the performance of hysterectomy. Three to four weeks should be the maximum. If the period of time exceed this, the fibrosis associated with the radium reaction will have taken place, and will render the removal of the uterus a more tedious and difficult operation.

If one exposure in a "border-line" case fail to effect sufficient improvement to warrant operation, it is extremely improbable that further treatment will improve the outlook from a surgical standpoint, as each successive treatment inevitably produces an increased fibrosis.

(2) *Carcinoma of the Body of the Uterus.* This condition is much rarer than carcinoma of the cervix, and the total number seen at the Radium Institute has not exceeded 2 per cent. of all the cases of uterine cancer treated. In etiology it differs from that of carcinoma of the cervix in two chief particulars; it is more prone to occur after the establishment of the menopause, and is most generally met with in nulliparæ.

Hysterectomy for cancer of the body of the uterus gives much more encouraging results than cancer of the cervix. Dissemination takes place slowly, is rarely very extensive, fixation of the uterus is a late feature, and its removal can usually be easily accomplished. On this account the immediate performance of a complete hysterectomy should strongly be urged upon patients directly the diagnosis of carcinoma of the body has been clearly established. If, however, the patient refuses to submit to operation, or the condition be inoperable, radium treatment should be carried out by the insertion of a tube of 100 to 150 mgrs. activity, screened with 1 mm. silver, into the cavity of the body of the uterus, an exposure of twenty-four hours' duration being given. Great care must be exercised in introducing the tube, as the carcinomatous infiltration of the uterine walls renders them extremely friable, so that their perforation might quite easily be caused if any undue force were used.

A general radiation of the pelvic cavity should be performed, as in the case of the treatment of carcinoma of the cervix. Some improvement usually follows on the treatment, but as the symptoms of carcinoma of the body of the uterus are not so manifest, troublesome, or painful as those of carcinoma of the cervix, the result to the patient is not nearly so striking, and it is sometimes difficult to induce them to submit to further exposures on that account.

In not a few cases of carcinoma of the body metastatic deposits on the vaginal walls are met with, and it is interesting to record that these deposits are extremely susceptible to radium therapy. They speedily disappear under appropriate treatment, and show but little tendency to recurrence.

PROPHYLACTIC IRRADIATION.—The use of prophylactic irradiation in cancer of the uterus is steadily increasing, and it appears likely that before long it will be a routine procedure in all operative cases. There are three periods at which prophylactic irradiation may be administered:

(1) Three or four weeks before the operation.

This is advisable in all "border-line" cases, as by its use the peri-uterine infiltration is often very definitely diminished, circumscribing its limits, and thus enabling the actual area of infection to be more exactly estimated. The irradiation, at the same time, will serve to bring about the degeneration, or inhibit the development of outlying foci of disease in the lymphatics.

(2) Two or three days before the operation.

This is of peculiar value in treating cases of the proliferative fungating type. The treatment should be administered two or three days before the operation. A tube of not less than 150 mgrs. activity, screened with 1 mm. of silver, should be introduced into the cervical canal, and an exposure of twenty-four hours' duration given. The irradiation obtained in this fashion will suffice to exert a lethal effect on any disseminated cells in the immediately surrounding tissues or lymphatics, but there will not be time for the development of a fibrotic change, which would serve to impede the performance of the major operation. As most of the tissues will be removed by the surgical procedure, only small isolated foci of the disease will remain, and these the radiation will probably have affected so powerfully as to produce their ultimate degeneration.

(3) Two or three months after the major operation.

This should be carried out as a routine measure in all cases where Wertheim's hysterectomy has been performed for malignant disease, but considerable caution must be exercised in its performance. The elaborate and extensive dissection which is associated with Wertheim's hysterectomy appears seriously to impair the functions of the trophic nerves of the pelvis, and some time elapses before these functions return to normal. Too heavy a dose given at too early a date may result in an excessive reaction, with the production of a recto-vesical or recto-vaginal fistula. On this account, therefore, it is advisable to limit the intra-vaginal treatment very considerably, not to treat the case until at least two months have elapsed, and then to use only a tube of from 50 to 70 mgrs. activity, screened with 2 mm. of lead, applied in the vagina in contact with the pelvic scar, the exposure to be of twenty-four hours' duration, preferably two periods of twelve hours each, with an interval of rest of twenty-four hours between.

A powerful irradiation of the pelvic cavity may, however, be given with perfect safety; 200 to 300 mgrs. of radium may be used, screened with 2 mm. of lead, and applied externally in such fashion as thoroughly to irradiate the whole operation area. The total exposure in this situation may be of twenty-four to thirty hours' duration.

RECURRENCES.—Patients suffering from recurrence after hysterectomy often do exceedingly well, more especially if treated within a short time of the appearance of the recurrence. The technique adopted is governed almost entirely by its position and shape. If nodular, and

situate at the vaginal vault or on the recto-vaginal septum, the actual insertion of a 50 mgrs. tube, screened with 1 mm. of silver, for twenty-four hours will often bring about disappearance, and recurrence is not very frequent. When the recurrence is situate on the anterior vaginal wall the proximity of the urethra renders the insertion of a tube into the mass a somewhat hazardous procedure, as it might be followed by the production of a fistula, and for this reason the treatment has to be carried out by means of a leaden screened applicator applied in contact with the vaginal surface of the nodule, supplemented by a smaller silver-screened tube applied within the urethra for two or three hours on four or five successive days. In this way fibrosis of the nodule with encapsulation of the enclosed cells is often obtained, and the risk of a vesico-vaginal fistula obviated.

When the recurrence manifests itself as a diffuse carcinomatous infiltration of the vaginal scar and upper part of vaginal canal, a 100 mgrs. tube screened with 2 mm. of lead and rubber should be inserted into the vagina and maintained in contact with the infiltrated area by light gauze packing. Flat applicators containing 150 to 200 mgrs. screened with 2 mm. of lead should be applied immediately above the pubes and in each iliac fossa The exposure in each situation should be of twenty-four hours' duration, and should be repeated at intervals of six weeks if necessary.

D.—DISEASES OF THE FALLOPIAN TUBES

Primary malignant disease of these structures is very rare, and is seldom diagnosed until the abdomen has been opened, and an exploratory operation performed. The pathological conditions most commonly met with are either acute inflammatory infections, or cyst formations, neither of which is suitable for radium treatment.

E.—DISEASES OF THE OVARIES

New growths of the ovary may be either cystic or solid, but the former are of much more frequent occurrence. Cystic tumors of any kind—innocent or malignant—are but little influenced by radium, and its use in these conditions is, therefore, of but little practical value.

1. *Papilliferous Cystic Disease of the Ovary.* In the late stages of this disease, when rupture of the cyst has occurred, and the peritoneum is studded with numerous secondary papillomatous growths leading to the development of hydroperitoneum, some transient benefit occasionally follows a prolonged exposure of from thirty to sixty hours' duration with flat applicators screened with 2 mm. of lead, and applied on the abdominal wall over the infected regions. If much fluid is present it is advisable to perform paracentesis before commencing the exposures. The treatment often serves to retard the progress of the disease, and lessen the rate at which the ascitic fluid accumulates. It cannot do more than this, however, and must be regarded only as a palliative.

2. *Ovarian Fibroids.* These growths are not suitable for radium treatment, and if giving rise to pain or other symptoms, should be removed surgically.

3. *Ovarian Carcinomata and Sarcomata.* The prognosis in cases of malignant disease of the ovary is most grave, and operative procedure should always be undertaken if possible. If this be impracticable for any reasons, prolonged exposures with applicators screened with 2 mm. of lead may be given. The applicators should be disposed on the sur-

face of the abdominal wall over the tumor, in such fashion as to procure a "cross-fire" radiation. The total exposure should be of from thirty to sixty hours' duration, the position of the applicators being changed every ten hours to prevent irritation of the skin. By these measures some retardation of the rate of growth, diminution of ascites and amelioration of pain, if such be present, may be obtained, but nothing more than this can be expected. In some cases no benefit whatsoever is observed; in others a definite response is noted, justifying a repetition of the exposures after an interval of six weeks.

F.—DISEASES OF THE URETHRA AND BLADDER

1. *Urethral Caruncle.* These growths are best treated by surgical measures, cautery or excision. It would be possible to effect their removal by a destructive reaction with a "full strength" applicator unscreened, but the pain attendant upon such a reaction would be greatly aggravated by the passage of urine over an inflamed and ulcerated surface, and on this account radium treatment is not to be recommended for the condition.

2. *Epithelioma of the Urethra.* Primary epithelioma of the urethra is occasionally met with in elderly females. It usually starts as a small nodule in the posterior wall of the urethra, which gradually spreads until it completely surrounds the canal. If operation be refused, radium treatment should be resorted to, as it will often produce a complete disappearance of the growth, and prevent its extension to the bladder, though it appears to have but little influence in checking dissemination through the lymphatics.

A 50 mgrs. tube, screened with 1 mm. of silver, is inserted in the urethra—which may, if necessary, be rendered anæsthetic with novocaine—and a total exposure of from eight to twelve hours is given in this situation, preferably in three exposures, each of from three to four hours' duration on three successive days This treatment is supplemented by the use of a 100 mgr. tube, screened with 2 mm. of lead and rubber, inserted into the vagina and maintained in contact with its anterior wall by light gauze packing. Here the total exposure should be from twenty-four to thirty hours' duration—three exposures each of from eight to ten hours' duration on three successive days. The resultant reaction is very slight, and occasions the patient but little discomfort. The growth and surrounding induration gradually diminish, sometimes completely disappear within a month or five weeks. Recurrences are, however, apt to occur after some little time, and on this account the patient should be examined at intervals of about three months, so that any recrudescence may be dealt with promptly.

3. *Papilloma of the Bladder.* Recurrent and inoperable cases of this disease are often very greatly benefited by radium treatment, the growths shrinking, their vascularity being diminished, and the hæmaturia arrested.

Flat applicators containing 100 to 150 mgrs., screened with 2 mm. of lead, are placed low down on the abdominal wall over the fundus of the bladder. A 100 mgr. tube, screened in similar fashion, is inserted in the vagina, and placed in contact with the under surface of the trigone. The exposure in this situation should be of from twenty to thirty hours' duration. If the patient is tolerant of intra-vesical instrumentation, a 50 mgrs. tube, screened with 1 mm. of silver, and mounted on the end of a silver wire stylet, may be introduced into the

bladder, and an exposure of from three to four hours' duration given on three successive days.

By this combined method of treatment an extremely powerful "cross-fire" irradiation of the whole bladder cavity is obtained, rapid and pronounced symptomatic benefit resulting. The series of exposures may have to be repeated after an interval of two months or so, but in favorable cases a period of a year or longer may elapse before the hæmaturia returns and further treatment is needed.

4. *Carcinoma of the Bladder.* Inoperable cases of this disease in which the patient is tolerant of intra-vesical applications, may quite justifiably be submitted to radium treatment, as great improvement, sometimes going on to apparent cure, may result. The treatment is identical with that indicated for papilloma of the bladder, but the exact position of the growth should be clearly determined by cystoscopy, so that the tube which is introduced into the bladder through the urethra may be placed in accurate apposition with the surface of the growth.

If a supra-pubic opening exists, and the tumor is of a size and shape which will permit of the actual burying of a tube within its substance, one or more tubes of 25 mgrs., screened with 0.3 mm. of platinum, may be embedded therein for a period of twelve hours. Definite symptomatic improvement is usually evident in about three weeks, and in the most favorable cases healing of the ulcerated area, with transformation of the carcinomatous material into a fibrous mass, takes place.

G.—NEUROSES

1. *Pruritus.* This is most generally met with in association with some definite pathological change in the skin of the vulva, such as lichenification or leukoplakia, and in these cases the treatment of the pruritus is that of the condition producing it.

There is, however, a pruritus which occurs in highly neurotic subjects, and in which no pathological lesion can be found as the exciting cause. These cases are most intractable, and radium often fails completely to bring about any relief. Even when it does prove effective, freedom from the complaint is seldom of long duration, and any slight nervous shock, exhaustion, or undue emotion will serve to bring about a return of the irritation. Short exposures of three to four minutes' duration with "half strength" applicators screened with 0.01 mm., should be given on three successive days, and repeated at intervals of three weeks. It is very advisable to avoid an exposure of a strength sufficient to produce vesication, as if this occurs the patient will be quite likely to attribute any subsequent trouble to the result produced by "the radium burns."

2. *Ovarian Neuralgia.* Patients who are approaching the menopause, and are of a definitely neurotic type, sometimes complain of severe attacks of neuralgic pain referred to the region of the ovaries, for which no adequate cause can be discovered by the most careful physical examination. Routine medical treatment often proves ineffective and radium sometimes gives great relief. Flat "half strength" applicators, screened with 2 mm. of lead, should be applied over the ovarian regions, and an exposure of three to four hours' duration given daily for a week, the series being repeated, if necessary, after an interval of two months. If the series be repeated on several occasions it is highly probable that premature induction of the menopause will result, but as the patients are usually approaching their climacteric when the neural-

gia first appears this possible sequel is not of very great moment. Benefit is often observed to follow the treatment above indicated, but it is highly probable that the results obtained are as much psychical as physical in origin.

I am greatly indebted to my colleagues, Dr. J. E. A. Lynham and Dr. Philip Gosse, for much generous help and valuable advice in the compilation of this report.

REPORT OF THE RESEARCH DEPARTMENT

By J. C. Mottram, M.B., D.P.H., Etc., Director

During 1920 increased protection for the radium workers was instituted, and as mentioned in the last report, evidence was being found of a return of the altered blood condition of the workers to the normal. During 1921 the evidence of this became very clear, and finally the details were published (*Archives of Radiology and Electrotherapy*, May, 1921, pp. 368-372). In the case of the red cells, the polymorphs, and the hæmoglobin the return to the normal was complete; only a mild lymphopoenia persisted. In this paper there is also a short description of the protective devices which gave rise to this desirable result.

The results of two other investigations upon the action of radium and x-rays on the blood have been published during the year:—

(1) In collaboration with Professor S. Russ, "Lymphopoenia following exposure of rats to soft x-rays, and the beta rays of radium," *Jour. Exp. Med., Sept.*, 1921, 34, pp. 271-273.

Hitherto moderately penetrating x-rays had been used to produce a lymphopoenia. Murphy (New York), using a very easily absorbed type of x-ray, had found a lymphocytosis. The present communication shows that this lymphocytosis is preceded by a transitory lymphopoenia, which was overlooked by Murphy, and which was found when beta rays as well as soft x-rays were used. The lymphocytosis is thus not a direct effect, but probably a reaction to destruction.

(2) "Observations upon the action of radium and x-rays on the mono-nuclear leucocytes of the blood of rats." *Jour. Roy. Soc. Medicine*, Pathological Section, Feb., 1922.

It had been observed that a lymphopoenia follows the x-radiation of rats, and that a second exposure has no effect on the lymphocytes remaining behind, and that only after the return of the mononuclears to normal numbers does a second exposure produce a second disappearance. It thus appears that there are two kinds of lymphocytes; one type sensitive to radiation, the other relatively insensitive. Measurement of the size of these cells before radiation, and of those left in the circulation after radiation, showed that the sensitive class are composed of small lymphocytes, and the insensitive of large. This conclusion was confirmed by observations made during regeneration, and upon animals suffering from a lymphopoenia due to their having been kept on a vitamin-free diet.

During the year a new line of investigation was begun in collaboration with Drs. Cramer and Drew of the Imperial Cancer Research Fund. As a result two papers have been published in the "Lancet."

(1) "Similarity of effects produced by absence of vitamins, and

by exposure to x-rays and radium." (The *Lancet*, 1921, I. 963).

(2) "On the function of the lymphocyte and of lymphoid tissue in nutrition, with special reference to the vitamin problem." (1921, 2, 1202).

The basis of this work has been an attempt to correlate the remarkable similarity between the effects of withholding vitamin beta and of exposure of animals to x-rays and radium. In both cases the animals lose all adipose tissue, the lymphoid tissues degenerate, a lymphopoenia is an early occurrence, the testes atrophy, the temperature and weight falls, and the animals die in a marasmic state.

The outstanding common pathological change is the degeneration of all lymphoid tissue, and the object of the investigation was to approach the subject simultaneously from the vitamin and the radium sides. A result of practical and therapeutic value may be especially mentioned. It has been found that resistance to radiation as measured by the lymphopoenia produced is increased by a diet rich in vitamin beta, and also that the recovery from the effect of radiation is hastened. It should, therefore, be beneficial to place on a diet rich in vitamin beta all patients who are undergoing prolonged irradiation.

The two hundred and twenty milligrammes of radium on loan from the Medical Research Committee for research work has been made use of in the above research, and is also being used in an investigation dealing with certain red cells changes, which are not sufficiently advanced for report.

REPORT OF THE CHEMICO-PHYSICAL LABORATORY

By W. L. S. Alton, F.I.C. Director.

The work of the laboratory for 1921 is summarized in a table giving the figures for 1920 and 1921:—

	1921.	1920.
Number of bottles of radium emanation solution distributed	3,800	4,800
Total output in litres	950	1,200
Number of emanation tubes and applicators prepared	719	765
Activity of above in terms of radium bromide.	73.244 grammes	65.235 grammes
Number of radium applicators prepared....	5	5
Number of measurements of radioactivity....	30	31

* * * * * *

It will be seen that the average strength of the tubes and applicators made was higher than in the preceding year, due partially to the use, within the institute, of radium salt tubes containing ten and twenty milligrammes of radium bromide. Two of these tubes have been made; others are in course of preparation, and it is advantageous to have some of these tubes always available for insertion into growths, instead of having to prepare emanation tubes for the purpose. The screens are of

platinum iridium, with a wall 0.3 mm. in thickness, length 14 mm., and diameter 1.5 mm.

For use outside the institute emanation tubes are supplied. The amount of radium used for the preparation of emanation applicators is sufficient for a weekly output, equal in activity to two grammes of radium bromide.

The steps taken for the protection of the workers from the effects of radium (see previous reports) have been beneficial. Early in the year, however, it was seen that the blood counts of the laboratory staff were not improving at the same rate as those of the other workers. Increased protection was sought, and it was decided to remodity the whole technique of the emanation apparatus. Protection by "distance," rather than by the use of heavy metal screens, seemed to be suitable, and the following modifications were made in the course of the year:—

The necessity of entering the strong rooms where the emanation pumps were kept was obviated by linking all the sets of radium solution bulbs to two lengths of glass tubing, drilling a hole through the fire-brick wall of the strong room, and joining up with two pumps in the adjoining room. By this means proximity to a large surface of glass coated with active deposit is reduced to a minimum, and the time spent on pumping is also shortened.

The apparatus for filling plates and capillary tubes was removed to a room at some distance from the central laboratory, the operator remaining in that room only for the time necessary for filling the applicators. These are then taken to another room (not the laboratory), and kept in a lead vessel with walls one inch in thickness, until ready for measurement. All returned apparatus is also kept in this room, the main object being to insure that no large quantity of active material should remain in any room occupied by the workers.

A suitable container for the transport of emanation tubes has been designed, giving protection both by distance and by screening, as shown in Fig 1.

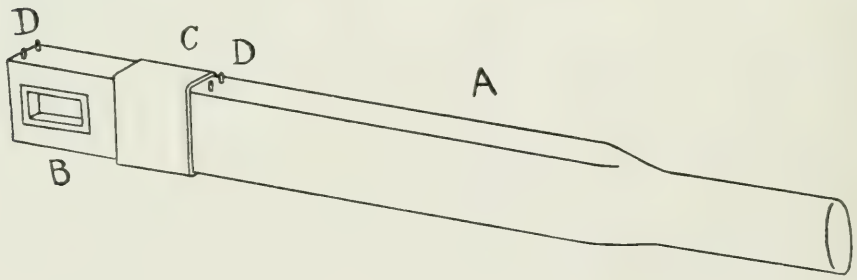

Fig. 1.
A. Wooden handle 18 in. long.
B. Recess of thick lead.
C. Lead sleeve, sliding between steel studs, D.D.

Grants of emanation have been made for lecture purposes, and for research work in other institutes, and demonstrations of the apparatus used can be given upon application.

A REPORT OF THE WORK AT THE MANCHESTER AND DISTRICT RADIUM INSTITUTE

From January 1st, 1921, to December 31st, 1921*

By Arthur Burrows, M.D., Radiologist.

The year has been one of transition in as much as the Institute has been transferred from the Manchester Royal Infirmary to a separate building where a complete hospital for radium treatment has been constituted. This transfer has brought about a number of changes and advantages, not the least of the latter being the provision of 13 beds which are used solely for radium treatment.

Between January 1st, 1921, and December 31st, 1921, 783 cases have presented themselves at the Manchester and District Radium Institute, with a view to Radium treatment. This shows a slight decrease over the previous year.

The Physicist reports that 526 emanation plates and 1,281 emanation tubes were made during the year.

Sixty cases of malignant disease, exclusive of rodent ulcer, were rendered free from signs and symptoms of the disease during the year. This includes four cases of carcinoma of the uterus previously inoperable which were rendered operable and the operation performed. As 564 malignant cases were treated, this 60 represents nearly 12 per cent. of the total number of cancerous patients seen, which proportion practically maintains the average of the year 1920. One case of carcinoma of the anus, five cases of carcinoma of the breast, 27 cases of carcinoma of the cervix of the uterus, seven cases of carcinoma of the mouth and tongue, 12 cases of carcinoma of the skin, 4 cases of sarcoma, 3 cases of endothelioma, and one other make up the 60 cases.

The number of rodent ulcers treated was 71, and 36 were apparently cured.

Twenty-four non-malignant conditions were cured. Thus, 120 patients were rendered free from signs and symptoms at the end of the year.

The total number of attendances of patients during the year has increased from 5,424 in 1920 to 6,167.

Professor Dean has undertaken to supervise the examination of the pathological material provided by the institute, and to conduct investigations of the condition of patients treated by radium from the pathological point of view. Since the opening of the institute in September, 41 specimens of morbid growth before and after radium treatment have been submitted to microscopical examination, and systematic examination of the blood of the radium workers and patients has been instituted.

Later in this report is published an analysis of over 2,500 cases which were treated at the institute between the years 1915 and 1919. Of these patients 1,753 were suffering from cancer, 267 from rodent ulcers, and 575 were suffering from various conditions which are usually described as non-malignant, although a considerable proportion of them

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will, if allowed to progress, terminate in death. This record shows that 135 cases of malignant disease, the vast majority of which was beyond operation, have been alive for periods varying from 2 to over 6 years, and remain well at the present time. The proportions of these are shown later in the report.

Rodent ulcers, benign tumors, exophthalmic goitre, uterine hæmorrhage, Hodgkin's disease, keloid, spring catarrh, and lupus vulgaris have all also shown a large percentage of gratifying results.

The technique of radium treatment is steadily improving, and it is to be expected that in the future the results of treatment will be still further improved.

EXAMINATION OF CASES TREATED, ETC., BETWEEN 1915 AND 1919

The total number of cases investigated during the above period is 2,595. This excludes those who although examined did not present themselves for treatment, and those so very advanced as to be hopeless even for palliation. Of this total 1,753 were cancerous cases, 14 cases of papilloma of the bladder, and 14 of mediastinal tumor. These last are included because they are generally borderline in nature and if left alone prove fatal. In addition 267 patients were suffering from rodent ulcers, and 575 were not malignant.

Practically all the cancer cases except those of the skin were inoperable, except a very small number which were treated by radium for special reasons, such as bad general health, failing heart, or diabetes. A certain number of cases of early carcinoma of the cervix of the uterus, treated immediately before operation, are included under the heading "prophylaxis."

Under these conditions 135 patients are alive and well today, having lived periods varying from 2 to nearly 7 years. This makes just over 7½ per cent. of the cancer cases treated. If we omit cases of skin carcinoma, although a number were inoperable, the percentage works out at 6¼.

There are two columns to the tables giving the numbers of cases (a) who were well for six months or more and then disappeared; (b) who were well for six months or more, but the growth subsequently recurred, or the death of the patient is recorded quite often from a different disease. It is not proposed to claim any of these cases as cures (except rodent ulcers), but rather to give them as good examples of excellent palliation, the test of effective palliation being a stringent one. Their numbers amount to 146, which is interesting, for it points out a fact which has been mentioned in one of these reports before, viz.: that about 50 per cent. of the symptomatic cures annually reported eventually recur.

The cases recorded under the heading "improved," "not improved," and "died," are classed together because, although a great deal of useful work is done in relieving suffering, the personal factor enters so largely into estimating what improvement is, while the figures given do not come into the main discussion except secondarily and as a group, of the curative value of radium in cancer.

To deal with the different forms of cancer in detail:—

CARCINOMATA

(1) *Epithelioma of the Anus.*—One case has been well between 5 and 6 years.

(2) *Carcinoma of the Breast.*—Two cases have been well between

6 and 7 years, 2 between 5 and 6 years, 2 between 4 and 5 years, 5 between 3 and 4 years, 5 between 2 and 3 years, and 1 inoperable case was eventually operated upon. More than half of the cases of carcinoma of the breast treated by radium are recurrences after operation.

(3) *Carcinoma of the Cervix of the Uterus.*—In this condition 2 patients have been well between 5 and 6 years, 1 between 4 and 5 years, 5 between 3 and 4 years, 5 between 2 and 3 years, and 8 previously inoperable were subsequent to treatment operated upon. In a number of cases after the operation the growth of the uterus was found to have completely disappeared. These figures include the cases treated before tchnique had improved to its present stage.

(4) *Carcinoma of Glands.*—Two of these cases have been well between 2 and 3 years. As a rule this condition is not a hopeful one, as the glandular infection is commonly extensive and secondary, or else it occurs in glands secondary to a primary growth which could not be discovered.

(5) *Carcinoma of the Lip.*—Of these cases 2 have been well between 4 and 5 years, 4 between 3 and 4 years, and 2 between 2 and 3 years. This represents 25 per cent. of the total treated.

(6) *Carcinoma of the Mouth and Tongue*—Of these patients 1 has been alive and well between 6 and 7 years, 1 between 5 and 6 years, 2 between 4 and 5 years, 1 between 3 and 4 years, and 2 between 2 and 3 years. The rapid formation of secondary deposits is an adverse factor in this condition, which, on the whole, is not a favorable one from the radium point of view; but the use of unscreened emanation tubes has improved results. In 29 of the cases treated the primary growth was caused to disappear.

(7) *Carcinoma of the Rectum.*—In this condition it is uncommon to get a really good result, and palliation is really the most that can be hoped for; but one patient has been alive and well between 5 and 6 years, and another one more recent than those recorded in the table has been to this date successfully treated.

(8) *Carcinoma of the Skin.*—Thirty-three of these cases have been alive and well between 2 and 7 years, which represents nearly 25 per cent. of the total treated. These cancers are not of their nature particularly susceptible to radium, but they are accessible, and it gives some indication of what might be done in the treatment of operable cases.

(9) *Carcinoma of the Thyroid.*—Two of these cases have been alive and well between 6 and 7 years, 1 between 4 and 5 years, and 1 between 3 and 4 years. If not too advanced this is a favorable condition for radium treatment.

(10) *Carcinoma of the Vulva.*—One patient has been alive and well between 5 and 6 years, 1 between 3 and 4 years, and 2 between 2 and 3 years. The burying of unscreened tubes in these cases is the most hopeful method of treatment at present, but it has one great drawback in that it is extremely difficult to keep the vulva clean, and the reaction is apt to be extremely prolonged and painful. Thus, all the cases treated have been very advanced ones, and in early cases, on the whole, surgery is likely to be a less painful method of treatment. Perhaps diathermy may obviate this difficulty in the matter of pain.

(1) *Abdominal Carcinoma.*—If in abdominal carcinoma there is widespread dissemination of the growth little can be hoped for from radium treatment. In 2 cases of carcinoma of the colon promising results were obtained. One case was without signs of growth for 2

years, but died subsequently of a recurrence, while another lived for 3 years in good health without symptoms or signs of the disease, but eventually died, according to information supplied, of cerebral hæmorrhage. Of course a possible alternative cause of death was a secondary deposit in the brain. Carcinoma of the stomach, if tubes are buried in the growth, will often diminish in size and the pain cease for a while, but no completely successful result has been obtained so far in Manchester. One tumor of the stomach diagnosed as carcinoma was treated by external applications of radium and cured, but as laparotomy was not performed and no close investigation of the growth could be made the case has been classed under the heading of chronic inflammation.

SARCOMATA

(1) *Lymphosarcoma.*—Two of these cases have been alive and well between 3 and 4 years. The immediate results of radium treatment are often brilliant, but usually the disease spreads elsewhere and eventually kills the patient.

(2) *Naso-Pharynx.*—Two of these cases have been alive and well between 6 and 7 years, 1 between 2 and 3 years.

(3) *Myeloid.*—This tumor, although not strictly speaking malignant in its effects, does not respond well to radium treatment.

(4) *Various.*—This heading chiefly includes spindle-celled sarcomata. These tumors react very sluggishly to radium, and prolonged, not too violent, treatment over a long period is necessary. In the end, however, they repay the trouble taken, for the prospect of cure is much greater than in the case of the small round-celled type, which locally under radium treatment seems almost to melt away and subsequently recur. Under the heading of this paragraph 2 cases have been alive and well between 5 and 6 years, 2 between 4 and 5 years, 3 between 4 and 5 years, and 4 between 2 and 3 years.

Endothelioma of the Parotid Gland.—Of these cases 1 has been alive and well between 6 and 7 years, 2 between 5 and 6 years, 2 between 4 and 5 years, 1 between 3 and 4 years, and 4 between 2 and 3 years. This represents over 30 per cent. of the cases treated, many of which were recurrences following operation. The percentage of cures in these cases is so high as to suggest that radium in the future, looking especially to the good cosmetic results, is likely to be the treatment of choice. In any case, if a surgeon operates on a case of endothelioma of the parotid gland, on no account should he attempt it without the help of radium, in case the operation cannot be completed without destroying the facial nerve, or for prophylaxis.

Papilloma of the Bladder (mostly advanced cases).—One has been alive and well between 6 and 7 years, 1 between 4 and 5 years, and 2 between 2 and 3 years.

Mediastinal Tumor.—One of these cases has been alive and well between 3 and 4 years.

Rodent Ulcer.—125 patients who were suffering from rodent ulcer have now been well for a period varying from 2 to 7 years. A very large number of advanced hopeless cases are treated, and, in fact, the first 20 to 30 who came to the Manchester Radium Institute in 1915 were of this nature, but still 50 per cent. of all cases are cured. If properly treated, recurrence is rare, and judging from the results of the re-examination of patients (only one case of all written to came back with a recurrence) it is probable that most of the 24 under the

heading "well for six months but disappeared" are still well, and our records show that most of the 8 under the next column died of another disease.

NON-MALIGNANT CONDITIONS

A number of these are very interesting and some of the results surprisingly good.

(1) *Exophthalmic Goitre.*—Fifty-two of these cases are recorded as cured, that is to say, all symptoms and signs of disease have disappeared, except sometimes some slight exophthalmos, for over 2 years, and only one recurrence is recorded. Many cases have already when they come for treatment definite myocardial failure, which may persist, and although the hyperthyroidism is cured they cannot be recorded as cured cases. The application of radium is a prolonged process and much patience is needed because the treatment may last from 2 to 3 years.

(2) *Hodgkin's Disease.*—The cases sent by physicians and surgeons for treatment by radium may be divided into those under 25 years of age and those middle-aged. The former give excellent results. Three of them have been alive and well between 6 and 7 years, 1 between 4 and 5 years, 3 between 3 and 4 years, and 1 between 2 and 3 years. The middle-aged cases seem almost hopeless except for a good palliation. Perhaps they are two different diseases.

Keloid and Vicious Scars.—These nearly always yield to radium treatment, and although some mark must always remain, many of the results are so good that 16 have been classed under the heading "cured." Treatment of this condition also tends to be rather a long process.

Spring Catarrh.—With care and perseverance radium cures almost all these cases. In fact, it is the only satisfactory treatment of this hitherto incurable disease.

Cavernous Naevus.—Fifty per cent. of these cases are cured practically without any mark remaining at the site of the tumor. Radium, if persevered with, always stops the growth of these nævi and reduces their size.

Capillary Naevi.—In the treatment of this condition the difficulty is to know when to stop. They can always be made paler, but if treatment is kept on too long telangiectases will appear. Occasionally a perfect result is obtained in a small lesion. Eight of such cases are recorded in the table.

Excessive Uterine Haemorrhage.—Radium is a specific for this condition. The Manchester Radium Institute records only one failure, and this patient did not submit to a second application. Two patients died of other causes. In middle-aged women the menses can be stopped entirely, but if by using a small dose the risk of the necessity of a possible second application of radium is taken, with young women menstruation often returns to normal, and cases are recorded in which they have married and had children subsequently.

Lupus Vulgaris.—Contrary to general expectation, a good proportion of lupus vulgaris cases, if not too advanced, can be cured by radium.

TABLE I. (1915-1919)

MALIGNANT TUMOURS

DISEASE	Well 2-7 years.	Well 6 months or more but not recently traced.	Well 6 months or more but later recurred or died.	Improved, not improved, or died.	Prophylaxis.	Total.
Carcinomata:						
Anus	1	—	—	5	-	6
Bladder	—	1	2	18	4	25
Body of Uterus	-	2		6		8
Breast	17	16	19	299	28	379
Cervix of Uterus	21	18	18	230	2	289
Colon	—	—	2	4	1	7
Glands	2	—	2	64	4	72
Larynx	—		1	11	- -	12
Lip	8	1	4	15	6	34
Mouth and Tongue	7	8	14	273	7	309
Ovary	—		—	8	—	8
Prostate	—	—	—	6	—	6
Rectum	1	1	—	70	3	75
Skin	33	10	6	85	3	137
Thyroid Gland	4	—	—	23	—	27
Vulva and Vagina	4	3	2	30	5	44
Various	3	—	2	81	2	88
Sarcomata:						
Lymphosarcoma	2	—	2	31	2	37
Naso-pharynx	3	3	—	8	—	14
Periosteal	—	—	2	36	4	42
Myeloid	1	—	—	5	—	6
Various (chiefly spindle-celled)	11	—	3	45	8	67
Endotheliomata:						
Parotid	10	1	2	11	2	26
Various	2	—	—	4	1	7
Tumours of Doubtful Nature:						
Papilloma Bladder	4	—	1	8	1	14
Mediastinal Tumour	1	—	—	13	—	14
Total	135	64	82	1389	83	1753

TABLE II. (1915-1919).

RODENT ULCERS

DISEASE	Well 2-7 years.	Well 6 months or more but not recently traced.	Well 6 months or more but later recurred or died.	Improved, not improved, or died.	Prophylaxis.	Total.
Rodent Ulcer	125	24	8	109	1	267

TABLE III. (1915-1919)

NON-MALIGNANT DISEASES

DISEASE	Well 2-7 years.	Well 6 months or more but not recently traced.	Well 6 months or more but later recurred or died.	Improved, not improved, or died.	Prophylaxis.	Total.
Benign Tumours	23	4	—	25	—	52
Exophthalmic Goitre	52	5	1	122	—	180
Hodgkin's Disease	10	—	—	26	—	36
Keloid and Vicious Scars..	16	—	—	39	—	55
Spring Catarrh	7	—	—	1	—	8
Chronic Inflammation	13	1	—	32	—	46
Cavernous Naevus	17	—	—	18	—	35
Capillary Naevus	8	—	—	33	—	41
Uterine Haemorrhage	17	5	—	3	—	25
Lupus Vulgaris	13	—	—	11	—	24
Skin Diseases (various)...	8	2	—	19	—	29
Various	1	—	—	30	—	31
Blood Disease	—	—	—	12	—	12
Chronic Super. Glossitis...	1	—	—	—	—	1
Total	186	17	1	371	—	575

SUMMARY OF TABLES I., II., and III. (1915-1919).

Cases Treated.	Well after 3-7 years.	Total treated.
Malignant	135	1753
Rodent Ulcer	125	267
Non-Malignant	180	575
Grand totals	440	2595

CLASSIFIED RESULTS (1921).

TABLE IV.

Well at end of year	120
Improved	278
Not improved	114
Died of their disease	25
Not suitable for treatment	54
Too early or abandoned treatment	144
Prophylaxis	48
Total	783
The number of cases registered during the year was.....	783

TABLE V. (1921).

CLASSIFICATION OF CASES.

DISEASE	Abandoned treatment and too early.	Well at end of year.	Improved.	Not improved.	Died.	Not suitable.	Prophylaxis.	Total.
Carcinomata:								
Anus	—	1	—	—	—	—	—	1
Body of uterus	1	—	—	—	—	—	—	1
Bladder	2	-	—	—	—	—	1	3
Breast	10	7	33	16	5	8	12	89
Cervix of uterus	56	27	16	12	3	10	11	180
Colon	—	—	1	—	—	1	1	3
Glands	5	—	6	12	1	—	—	24
Larynx	1	—	1	1	—	—	—	3
Lip	—	-	5	—	—	—	2	7
Mouth and Tongue	16	7	26	27	5	11	6	98
Ovary	—	—	2	—	—	—	—	2
Prostate	—	—	—	1	—	2	—	3
Rectum	9	—	5	6	—	2	1	23
Skin	3	12	14	6	1	1	4	41
Thyroid gland		—	2	1	1	-		4
Vulva	2	1	2	1	-	1	2	9
Various	2	—	6	4	1	4	—	17
Sarcomata	9	4	12	8	2	10	4	49
Endotheliomata	—	3	1	1	—		2	7
Mediastinal Tumour	—	—	2	1	4	1	—	8
Rodent Ulcer	6	36	25	4	-	—	—	71
Papilloma of Bladder	—	1	—	-	1	—	2	4
Benign Tumours	4	11	5	1	—	—	-	21
Keloid	3	—	9	—	—	—	—	12
Exophthalmic goitre	1	—	23	3	—	-	—	30
Naevus	5	—	21	6	—			32
Hodgkins' disease	—		2	1	—	-	—	3
Skin diseases	1	3	7	1	—	1	—	13
Uterine haemorrhage	4	8	—		—	2	—	14
Chronic inflammation	—	1	4	1	—	—	—	6
Blood diseases	—	—	2	—	1	-	—	3
Various (non-malignant)	1	—	1	—	—	—	—	2
Total	144	120	278	114	25	54	48	783

RADIUM TREATMENT OF MYOMA OF THE UTERUS AND MYOPATHIC BLEEDING

FINAL RESULTS IN ONE HUNDRED EIGHTY-THREE CASES*

By C. Jeff Miller, M.D., F.A.C.S., New Orleans

No abdominal operation has reached a higher degree of technical perfection or given more satisfactory postoperative results than hysterectomy as usually performed for myoma of the uterus. It is generally conceded that the results, both primary and secondary, hardly permit of improvement. For these reasons it is difficult to convince the surgeon that any other method of dealing with myoma of the uterus and hæmorrhage of myopathic origin can compete with the already standardized surgical procedures. Any other method of treatment must present properties rarely possessed by a therapeutic agent, and the results obtained by such a remedial agent must show that the relief is permanent, and that its use is safer than operation and gives a higher percentage of preservation of physiological function than an operation performed by a skillful surgeon.

That we possess in radium such a therapeutic agent, and that it will eventually supplant surgery in a large percentage of cases now treated by hysterectomy, I propose to prove by submitting the final results obtained in 183 cases treated with radium and observed over a period of 7 years. Between May, 1914, and July, 1921, 230 cases were treated by radiation, but satisfactory follow-up records are available in only 183 cases. It is useless to dwell upon the effects of radium, or the primary clinical results, since these phases of the subject are already definitely established, and about them there is little doubt. These records are of value chiefly because of the time that has elapsed since the treatment was instituted.

Since it may be inferred that I am over-enthusiastic in regard to the use of radium, I would make this point clear in the beginning by stating that during the same period of time which this report covers nearly an equal number of cases have been treated surgically. Thus it can be clearly shown that I appreciate the limitations of radiation, and am by no means insistent that it can supplant surgery in all cases of myoma of the uterus or essential hæmorrhage. The age of the patient, the type and social situation, as well as the size of the tumor, the condition of the appendages, the evidence of previous infection, and the general condition of the patient, are all factors to be carefully weighed in determining the most satisfactory method of treatment.

Surgery is unquestionably the procedure of choice in young women who present definite growths causing excessive bleeding, submucous growths, or cases in which suspicion exists of malignancy of the fundus of the uterus. In these types of cases conservative surgery is decidedly less radical; this is a point that cannot be too strongly emphasized. In order to induce shrinkage or disappearance of a myoma, it is necessar to produce at least a temporary cessation of menstruation, and the dosage of radiation has not yet been so controlled that a temporary sup-

*Reprinted by permission from Surgery, Gynecology and Obstetrics, xxxiv, 593-597, May, 1922. Read at Southern Surgical Association, Pinehurst, North Carolina, December, 1921.

pression can be foretold with the degree of accuracy necessary for justifying its use when conservation of function is of primary importance. Therefore, in young women, when definite single tumors are present, the patient should be persuaded that operation offers a chance for myomectomy, with preservation of the physiological functions. In small multiple growths, when it can be definitely established beforehand that hysterectomy is necessary, radium should be adopted as the method of choice.

The most striking feature revealed in a review of both series of cases, those treated by radium and those treated by surgical intervention, is the increasing percentage of myomectomies performed, where formerly hysterectomy would have been done. The prevalent idea that myomectomy is attended with a high mortality and that second operations are necessary in too large a percentage of cases to warrant conservatism is not borne out by the results obtained by competent surgeons. The decision to resort to myomectomy in many cases which would have been subjects for hysterectomy formerly was prompted by the assurance that if myomectomy failed to control the hæmorrhage or check the menstrual disorders, radium would complete the cure without further surgical interference. With such assurance, the scope of conservative surgery has been materially widened, a larger number permanently relieved, and the percentage of subsequent pregnancies has further justified the decision.

Large myomata should be treated by myomectomy or hysterectomy. Unless some contra-indication to operation exists, there is no valid reason for the use of radium in large tumors. Massive growths too often present serious complications such as adhesions, salpingitis, degenerative changes, and pressure symptoms, to prompt the surgeon to depend upon radiation as the method of election.

Radiation has, however, a distinctive application in this group in that it will promptly control the hæmorrhage until such time as the consequent improvement in the patient's general condition will render her a safe operative risk. Radium is a valuable adjunct to surgery in this group, but it should seldom be the elective treatment in myomata larger than a three and a half months pregnant uterus. Upon this point the majority of observers generally agree, large growths only partially shrink, and the period of treatment extends over too long a time to satisfy either the physician or the patient. Therefore, in cases of this group radium should be used only in exceptional instances.

One hundred and seven of the 183 cases of this series presented myomata varying in size from small tumors detected during the course of diagnostic curettage to ascertain the cause of bleeding, to massive growths extending above the umbilicus. There were only a few of the latter group treated, and practically all of them presented contra-indications to operation. The ideal type for treatment with radium is the small or moderate sized interstitial myoma. The primary result is uniformly prompt, and recession in the size of the growth, while variable, is sure. The diminution is usually more than 50 per cent. The growth is frequently reduced to a negligible affair, and often entirely disappears.

Submucous growths, while responsive to radiation, should be selected with extreme care, owing to their known tendency to infection and sloughing after intra-uterine manipulations. In our series two of the earlier cases of this type developed pyometra, and one of them eventually required a hysterectomy. The size of subperitoneal growths is influ-

enced least of all, and it has also been noted that radium has less effect in reducing the size of myomata in women beyond the menopause. Our best results appear to have been obtained in women presenting a history of severe menorrhagia.

It is apropos to mention here the technique followed in the application of the radium. Preliminary curettage should precede the application in order to permit a careful bimanual examination under anæsthesia, to eliminate small polypi, and to provide for a microscopic examination of the uterine scrapings.

The radium is introduced into the cavity of the uterus screened by brass and rubber or frequently a celluloid capsule, and is left in situ from 3 to 24 hours, according to the indications. The average time of exposure in our series in young women—those under 38 years of age —was 12 hours in cases of myomata. In women beyond this age, where it was not so important to preserve menstruation, the treatment lasted 24 hours. As a rule, 50 milligrams of the radium element was employed. This dosage produced permanent cessation of menstruation in women over 40 years of age in 94 per cent. of the cases. In our earlier work a second exposure was made within 10 days or 2 weeks, but it was soon observed that this was unnecessary, and often caused discomfort that was persistent, and occasionally very distressing.

At present we believe that one application is sufficient, and that subsequent exposures should be given only as indications develop. The recession in the size of the growth may be surprisingly rapid, or it may be gradual. Again, the growth may appear unaffected for several months, and then suddenly show a rapid shrinkage. For this reason, repeated exposures should be cautiously advised, and repeated examinations should be made to check the status of the tumor. Lately we have preferred to make 15-hour exposures, and to repeat the application in 3 or 4 months if it is necessary. We have found that, even after reducing the exposure, the single application is usually sufficient. This permits of its use in younger women, since our experience has shown that in many cases menstruation will reappear in several months, or as late as 2 years, and continue normal thereafter. Furthermore, the menopausal symptoms are apparently less marked when the shorter exposures are employed.

One hundred and two of the 107 cases reported complete relief from hæmorrhage within 5 months after radiation. Two of the remaining five required a second application before being relieved. Two others were not relieved by a second exposure, and the remaining case was eventually subjected to hysterectomy in another clinic. These figures practically correspond with the results obtained by other observers, and prove conclusively that no other agent at our disposal equals radium in controlling excessive uterine bleeding.

It has already been mentioned that the effect on the size of the tumor is variable. Fifty-seven cases returned within 5 years for other conditions, or for examination. In 37 of these the growth could not be determined at the subsequent examination, or was so reduced as to be classed as negligible. In two instances massive growths, as large as a 7 months' pregnant uterus, had shrunk below the umbilicus. Radium had been used in order to control bleeding because these patients were temporarily bad surgical risks. Both were sufficiently improved by the treatment to permit of successful operation at a later date. Reports were obtained from the balance of the series either directly from the

family physician, or from the patients, who reported the findings of their medical attendants, and these records practically correspond with those in the cases under my personal observation.

In outlining the limitations of radium, too much stress cannot be placed upon eliminating chronic pelvic infection. Latent infection is so prone to be fanned into activity by radiation that no case is selected for this treatment when doubt exists as to its presence. In four cases in this series, all of which occurred in our earlier work, this truth was not appreciated. In two cases pelvic suppuration followed, requiring vaginal drainage; one required a hysterectomy after a prolonged siege of pelvic peritonitis; and the fourth case was an invalid over a period of several months.

It was further noted that patients who complained of pain associated with myomata were not usually relieved of that symptom even when bleeding was controlled, and the tumor partially reduced by radiation. This symptom is frequently attributed to pressure, but certainly pressure cannot always be the cause, else the pain would disappear as shrinkage occurs. This has happened so often that now we usually advise the patient that the bleeding will cease, the tumor may shrink, but that we cannot promise that the pain will be relieved.

Seventy-six of the 183 cases were instances of myopathic hæmorrhage such as are commonly classified as chronic metritis, hyperpalsia, fibrosis, uterine insufficiency, and so forth, conditions most frequent in women approaching the menopause. In this type, radium more nearly approaches the ideal specific than any therapeutic agent at our command. Formerly, hysterectomy was the only satisfactory method of dealing with these conditions. At present it may be stated without exception that the surgeon who advises hysterectomy in uncomplicated cases of this group, when radium is available, is hardly acting in the best interests of his patient.

Fifty-eight cases of this last group were between the ages of 38 and 54 years. More than half had been subjected to all the measures usually employed, except hysterectomy. All received practically the same dosage, viz., a 24 hour exposure from a tube containing 50 milligrams of the radium element, as all of them had arrived at the age when it was not essential to preserve the physiological function. Four of them required a second application within 2 years for recurrent hæmorrhage, and were eventually cured.

Eighteen cases were between 15 and 36 years of age, 5 of them being between 15 and 18. The five instances of severe hæmorrhage in the women between 15 and 18 are of special interest. All had been treated by rest, tonics, glandular extracts, and repeated curettage without relief, and the hæmorrhage was so severe in one case that preparations had been made for transfusion. Three to 8 hour exposures with 25 milligrams of the radium element produced a temporary amenorrhœa, and menstruation was re-established in all cases within 14 months In four cases it was perfectly normal. Since we do not know the ultimate effect of radium on the ovarian structures, it should be used only as a last resort in women of this age. In the cases reported it was used only after every other measure had failed to give relief, and the final results were a signal triumph for radiation.

Of 18 cases under 35, in which it was desirous of controlling bleeding without producing permanent cessation of menstruation, radium was applied from 8 to 12 hours until from 200 to 800 milligram-hour expos-

ures were given. Six ceased to menstruate promptly; 4 of these reported a return in 1 year, which in one case was quite profuse; in the other cases it was perfectly normal. Five cases continued to menstruate scantily, the flow lasting the normal duration of previous periods. In four instances the flow was reduced and remained regular. Three cases menstruated irregularly, reporting scanty periods every 2 or 3 months.

Three pregnancies were reported in the series. One woman was delivered of a premature healthy baby at 8 months. The second case aborted at the fourth month. The third case is now 8 months advanced in pregnancy. An interesting feature of the cases of pregnancy is that in two instances there had been a period of sterility preceding the treatment, in one case of 3 years, in the other of 8.

When it was desirous of controlling bleeding in women over 40 years of age and full dosage was used, immediate cessation of menstruation followed in 20 per cent. of the cases. Sixty per cent. menstruated once, 15 per cent. menstruated irregularly, and the balance reported no relief and have since returned for a second treatment. The second treatment was successful in all but three instances, and two of these three were relieved by a third exposure.

Profuse leucorrhœa was noted in about 20 per cent. of the cases, and a slight but persistent discharge was reported in 30 per cent. In about 40 per cent. it was absent, or was so slight as to cause no comment. Not infrequently radium cured or markedly diminished a leucorrhœa which was present before its application. The leucorrhœa as a rule rarely lasted longer than 6 or 8 weeks, but in several instances it was persistent after a year.

A few of the patients were operated upon subsequent to radiation. Four of them had radium preliminary to operation in order to improve their status as surgical risks. Two developed pyosalpinx and both required hysterectomy. Two continued to complain of pain and submitted to operation for relief. Two others became discouraged and submitted to operation before sufficient time had elapsed to test the effects of radium.

Subsequent reports as to the menopausal symptoms are interesting. In women over 40 in whom preservation of function was not considered important, about 60 per cent. reported flushes and the usual phenomena of the climacterium. In about 20 per cent. the symptoms were reported as severe, and almost invariably these cases had given a history of bleeding of the aggravated type. The duration of symptoms lasted about the time of the normal menopause, but in two cases the flushes were very severe and have persisted for 6 years. The patients in their latest reports state that the flushes are as frequent and as severe as they were during the first 4 months following radiation.

This brief review of cases extending over a period of 7 years reasonably warrants the conclusion that a large percentage of the cases of myoma of the uterus formerly subjected to operation can be permanently and safely relieved by radium, and that practically all cases of uncomplicated essential hæmorrhage can be cured by radium.

MODERN TREATMENT OF CANCER OF THE LIP*

By Henry K. Pancoast, M. D., Philadelphia.

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Ever since radiation was first recognized as a possible curative agent against cancer, the surgeon has referred the inoperable and most advanced cases to the radiologist for treatment. Its use was at first regarded as an experimental measure, and, as we must all confess, also a convenience at times. The radiologist accepted such cases and proceeded to do what he could for them. At first the outlook was practically a hopeless one, but even though failure seemed the rule and a result in any way favorable the great exception, and criticism re-echoed the word "failure," the cases continued to be referred, and something had to be done for them. The radiologist did not become discouraged because he realized the possibilities in development of an apparently limitless field for research.

As a result, this branch of medicine has developed more rapidly than any other during the past 20 years. This is due in a large measure to the fact that radioactivity and the production of x-rays have been subjects of unusual interest to the physicist, in whose investigations the radiologist has recognized the solution of many of his problems. Naturally the bonds of mutual interest between the two investigators have grown stronger with years of co-operation. The highly competitive business proposition involved in the manufacture of apparatus has been of great assistance. The radiologist is calling upon the pathologist more and more for assistance that will lead to a better understanding of malignancy and the effects produced by radiation. Much knowledge is yet to be gained from investigations by the biologist and therein seems to lie the greatest field for activity in the near future. Co-operation with the surgeon will continue to be sought.

It must be apparent, therefore, that the radiologist is endeavoring by every possible manner of investigation to contrive means of accomplishing what surgery has failed to do. That he has been successful in some measure must be conceded. There is probably more that can yet be accomplished. A large part of the imposed task of successfully treating advanced malignancy must be acknowledged as impossible. It is sometimes difficult to draw the line sharply between the rarely possible and the impossible type of case, but such a line is important in order that the use of radiation treatment may not fall into disrepute in the lay mind. No doubt much of the innate fear of the knife has originated from the attempt of surgery in the past to try what it could not hope to accomplish in the cure of malignancy.

The radiologist probably sees more of the worst wrecks wrought by cancer than anyone else, and when he realizes that each case began in a small way at a period when the lesion, in most instances, could have been readily cured by surgery or by the proper use of non-surgical measures, he is appalled by the now existing general lack of recognition of cancer at its early stages, the failure to treat such cases at the most op-

*Reprinted by permission from Surgery, Gynecology and Obstetrics, xxxiv, 589-593, May, 1922. Read before the Clinical Congress of American College of Surgeons, Philadelphia, October, 26, 1921.

portune time, and the apparent disregard of preventive measures that will tend to eliminate recognized exciting causes of cancer in such localities as the lip and buccal cavity. It seems that the education of the lay mind and the physician to the realization of the importance of recognizing cause and early effect is woefully lacking. How often do we still see the jagged tooth digging into the cancerous area in the tongue or cheek, and even worse, the well-developed epitheliomatous ulcer of the cheek that has been repeatedly stimulated by applications of nitrate of silver.

Radiology has taken up no fight against surgery, nor does it regard surgery in any way as a competitive measure. It has been forced to develop a technique that will in a measure deal with some of the cases in which surgery is impossible, and in doing this, it expects some recognition. Naturally it can, as a rule, deal more successfully with borderline cases than with the more hopeless ones. Having gone so far, we, as radiologists, feel that if we can produce proof of just as successful results as surgery in what have been generally recognized as operable cases in the past, it is our right to treat such cases also. Naturally we shall aim to produce better results than surgery whenever possible, but above all, the best interests of the patients are always to be uppermost in our minds. Co-operation between the surgeon and radiologist is frequently of paramount importance. Radiology may be employed as an ante-operative procedure in conjunction with surgery, or as a post-operative measure. It is a well-recognized fact that radiation cannot do well in what surgery has tried to do and failed. The recurrent case after operation does not respond as well as the primary case because we have to deal with anatomical, physical, and biological factors that are quite different.

There are three recognized agencies for dealing with cancer at the present time: preventive measures, surgical procedures, and non-surgical methods. Preventive measures are more widely applicable about the mouth than any other locality. Proper attention to the teeth can unquestionably prevent many cases of cancer or precancerous conditions. The regulation of the use of tobacco may help in cases showing a tendency to leucoplakia. When syphilis seems to be a possible factor, antisyphilitic treatment should be pushed energetically, but too much valuable time should not be expended solely on such a measure when the lesion does not appear to respond. Leucoplakia should always be carefully watched and treated if necessary, and cracks and fissures on the lips should not be allowed to persist.

It is not our purpose to discuss surgical measures except from the standpoint of co-operation with non-surgical methods. The non-surgical methods which are now generally recognized as applicable in the treatment of lip and mouth cancer and its metastasis are the use of radium, the x-rays and electrothermic coagulation, or possibly the actual cautery. In many instances all of these agents must be combined and frequently with surgery. In comparatively few instances is any one of them employed alone.

Cancers involving the regions designated may be roughly grouped into lesions involving the lower lip and corner of the mouth, the tongue, primary lesions in the floor of the mouth, the tonsil, and in the mucous membrane covering the cheeks, the alveolar processes, the palate and pillars. The disease in each of these anatomical structures requires separate consideration. Mainly for obvious anatomic reasons the upper

lip is not included except when the disease involves the portion near the corner of the mouth. From the standpoint of a radiologist, the essential purpose of this paper must of necessity be the presentation of the present status of non-surgical methods of treatment.

THE LOWER LIP

The radiologist is probably not so much concerned as he should be in distinguishing between epidermoid and basal cell cancer of the lip. He realizes what the worst outcome may be and treats all cases with that idea in mind. He sees too often the results of direct surgical trauma to cancerous tissue and is loath to satisfy his curiosity by pathological proof of the cellular characteristics of a lesion unless certain that the removal of a specimen is absolutely safe.

Theoretically, lip cancer should be readily cured by surgery because both the primary and metastatic lesions are easily accessible, but this is not the result practically, mainly because surgery does not always remove all the cancer and a large number of cases are not seen sufficiently early. Surgical results would be ideal if some means of education could inculcate in the mind of every individual that every ulcer, fissure, or keratosis of the lip persisting for several weeks, especially if showing induration, and if syphilis be excluded, is either cancerous or potentially cancerous, and that such an area should be removed. The vast majority of lip cancers have, unfortunately, gone beyond this stage when first seen. The general run of cases as we see them may be divided into three groups, from the standpoint of methods of treatment, prognosis, and statistics, as follows: primary lesions without any evidence of metastasis; cases presenting small palpable nodes in the submental or submaxillary triangles; and those with advanced primary lesion and large nodes in these areas or in other gland groups. The greatest danger from cancer of the lower lip is metastasis, which, if it has occurred, increases the death rate very considerably. In view of the frequency of metastasis every one who treats such cases by any method should have an intimate knowledge of the lymphatic drainage from the lip. Lymph vessels pass directly downward from the central portion to the glands in the submental triangle, and from the lateral portions to glands in the submaxillary triangles. The submaxillary salivary glands are well surrounded by lymphatics. If there is blockage in the lymphatics of one side from cancer or some inflammatory process, the free anastomosis with the opposite side readily permits metastasis to pass from one side to the other. After involvement of these groups of lymphatics, metastasis may proceed to others in the neck.

In the first group of cases, without palpable nodes in the neck, the results of surgery are good. Metastasis without palpable evidence is likely to be present in a certain percentage of these cases, however, and surgery alone cannot be complete without including the removal of all glands in the submental and submaxillary triangles. Broders[1] in 1920 presented statistics on 449 cases operated upon at the Mayo Clinic and in which lymph nodes were removed, and metastasis was found in 23.38 per cent. At best, the results of surgery are little more than 90 per cent. of cures after 5 years. Sistrunk[2] in a recent communication presented statistics of cases of cancer of the lower lip operated upon at the Mayo

[1]Broders. Squamous-cell epithelioma of the lip. J. Am. M. Ass., lxxiv, 656.

[2]Sistrunk, W. E. The results of surgical treatment of epithelioma of the lip. Ann Surg., 1921, May, p. 521.

Clinic during 1912, 1913, 1914. Of 93 complete cases in which the primary lesion was excised and glands in the triangles removed and found not involved, 90.3 per cent. were living 5 to 8 years after operation. In eleven of these local recurrences were subsequently removed and there were three recurrences in neck glands.

The striking feature in these and many other statistics is the frequency of local recurrence, which indicates an incomplete removal of the primary lesion, leaving in situ cancer cells which have ample time to cause metastasis while the recurrence is developing to discoverable proportions. Obviously the results should be better, and surgery alone cannot be regarded as a complete method of treatment in view of our present knowledge of the effects of radiation. Many surgeons are satisfied to employ it as a postoperative measure. The wisdom of this is not borne out either by results or by scientific knowledge of the effects of radiation. It is our firm belief that every case should have at least a preliminary application of radiation before any attempt at removal of the primary lesion of lymph glands is attempted. We have not advocated non-surgical measures alone until a technique was developed which we believed was safe and certain of results. Too few cases have passed the five year period to make our statistics of value, but we are well satisfied so far with the results we have obtained.

Our technique comprises a preliminary radiation of the area of the primary lesion and well beyond all apparent evidences of involvement by radium. Cross firing is practiced as far as is possible, and we aim to produce a severe reaction. At the same time the region of lymphatic drainage is well radiated by radium, across the face from the level of the posterior aspect of one submaxillary salivary gland to the same point on the opposite side. A full dose of x-rays is then given over each side of the neck, and as the submental and submaxillary triangles are not apt to receive their full share of the dosage because of the protection of the mandible, these areas are given an additional dose of radium. This additional dose of radium produces a severe but not dangerous reaction. If the case is being thus prepared for the surgeon, we advocate waiting for the reaction to have reached its maximum and to subside slightly before operation, in order that the maximum effect upon the lymphatic channels as well as cancer cells may be brought about. If the case does not come from the surgeon, we proceed immediately to destroy the primary lesion by electrothermic coagulation, for two reasons: to obtain the added advantage of heat and to relieve the patient of the discomfort resulting from the severe radiation of the primary lesion. When a large mass of tissue is thus removed, there is some danger from secondary hemorrhage when the slough separates, and the patient is instructed how to stop the bleeding by pressure. Patients suffer little or no pain and there is only the annoyance from the sloughing process. Healing is complete in 2 weeks to a month. Usually there is insufficient deformity to require subsequent plastic surgery. As this procedure does not entail possible surgical trauma to cancerous tissue we do not fear the possibility of metastasis appearing later. The radiation of the neck is repeated once or twice at subsequent periods.

In dealing with cases belonging to the second group we have practically discontinued giving postoperative radiation, unless it is employed as an anteoperative measure as well as the results do not warrant its use. Cancer tissue once directly traumatized by surgery without a com-

plete removal and without previous radiation does not respond well to any form of treatment, and all too frequently upon the radiologist is laid the blame for inefficacy of radiation. If we are expected to treat cases at all, we should surely be accorded the privilege of directing that treatment along such lines as our experience shows to be the most effectual. The technique we now employ in cases belonging to the second group deals with the primary lesion, lymph-channel areas, and glandular regions in exactly the same way as in the first group, with destruction of the primary lesion by electrothermic coagulation. If the enlarged glands do not subside or do not diminish with reasonable rapidity, we may either try radium implantation or refer the case for block dissection, in which case we may regard the treatment already given as an anteoperative procedure. If the case is referred to us by a surgeon, the anteoperative treatment is given in the same manner as for group one cases, and the case is then referred back for excision and block dissection as soon as the reaction has subsided somewhat. It is then referred to us subsequently for postoperative treatment.

In this connection we are quite in accord with the procedure advocated by Quick[1] of embedding emanation tubes in the operative wound at all suspicious areas, and especially where lymph channels have been cut or cancer tissue has inadvertantly or of necessity been cut into and not removed in entirety. The resulting slow radiation and intense local but not far reaching action from beta radiation must certainly be efficacious, and entails no danger to the flap if the emanation seeds are well covered. One must use care in giving postoperative radiation following this procedure. We have not had the opportunity of following this technique because of the lack of an emanation plant at our disposal. The frequently flaunted objection of anteoperative radiation making the operation more difficult seems to be without good foundation, according to the statements of those who employ both radiation and surgery, especially if the operation is not performed at the time of the reaction.

We do not wish to go on record for the origin of a broad statement to the effect that cases of cancer of the lower lip, without metastasis or with early metastasis can be handled satisfactorily by nonsurgical methods, for the reason that such a broad statement is subject to too much latitude in its interpretation. We do believe, however, that such cases can be handled in a perfectly satisfactory manner by nonsurgical methods alone or in conjunction with surgery, but we absolutely insist that the technique carried out must be one similar to the one we have advocated, and that each procedure must be rigidly carried out to the most minute detail.

Cases belonging to the third group, with advanced primary lesion and extensive glandular metastases comprise an unfortunate class of mortals whom no one cares to handle. They usually fall to the lot of the radiologist to treat. The choice between surgeon and radiologist is practically one between two evils. Surgery cannot help, and usually makes matters worse. Radiation usually can do no better but is preferable. Implantation of radium into glandular metastases that have usually infiltrated through gland capsules is practically an imperative part of the procedure of radiation.

[1]Quick, Douglas. The conservative treatment of cervical lymphatics in intraoral carcinoma. J. Am. M. Ass., 1921, Aug. 6.

RADIOTHERAPY OF MALIGNANT TUMORS*

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The report which I present to you regarding the actual state of roentgentherapy can only deal with the broad outlines. I leave aside the technique and its brilliant development up to the present and limit myself to the consideration of three questions which are of particular importance.

The first question is of a very practical sort. What is at this time the part of x-rays in the healing of malignant tumors? To what extent should we take them into account to fix our therapeutic indications? Within what limits should we submit to roentgentherapy the cases which we have formerly operated?

To begin with, it should only be a question of the operable cases, that is to say, operable cancers. It goes without saying also that along with the success of the x-rays, we must also take into account that of radium. In spite of irrefutable theoretical considerations on the basis of which a massive homogeneous irradiation with strongly filtered x-rays is preferable to the more narrowly localized action of radium, in practice we cannot get away from radium, and experience has more than once demonstrated that the combined employ of its rays and x-rays gives better therapeutic results. That cancer of the skin and cancer of the lips could be healed by x-rays has been confirmed again and again since the first observations of Magnus Moeller in 1898. In these later times in cases of this sort, more penetrating and more heavily filtered rays have been used with advantage; remarkable results have also been obtained with radium. All of this success, it may be necessary to exclaim loudly in spite of contradictions, concerns both the prickle-celled epithelioma as well as the basal celled epithelioma. From the esthetic viewpoint in many cases the result is truly ideal and in this regard notably superior to that of operation. The idea that there was only an apparent healing, superficial cicatrization with persistence of cancer cells in the depth, must be abandoned. There are numerous observations on cancers of the skin and cancers of the lips where the healing has persisted for three years and longer.

Undoubtedly roentgen or radiumtherapy would always be preferred to operation for cancers of the skin and lip, if this ideal healing could always be obtained with certainty. Such unfortunately is not the case. It happens that the x-rays, after having caused the disappearance of the principal tumor leave a portion of the lesion which, when it again begins to grow, proves insensible to their action even though the same technique is employed which is so efficacious at the start. Sometimes radium will give a result when it cannot be obtained with x-rays, but often the recurrences are refractory even to the rays of radium. In cancer of the lip, according to statistics, the proportion of cures after three years amounts to 80 per cent. either with radiation or operation. In the treatment of cancer of the lip, as also that of the skin, I consider it proper to give the preference to radiotherapy, and it seems to me that

*Herewith is presented a translation of the splendid paper presented by Professor Perthes, Director of the Surgical Clinic at the University of Tubingen at the Congress of the German Surgical Society, April 2, 1921 This article is a translation of the translation in French by Dr A. Beclere, which appeared in the March, 1922 issue of the Journal de Radiologie et D'Electrologie.—Ed.

certain conditions, such as advanced age or concern regarding the esthetic, make a formal indication for this preference, providing the patient is kept under careful observation.

For cancer of the penis, even more than for that of the face and lips, we have an inclination to prefer radiumtherapy. Keysser of Jena was able to avoid the amputation of the penis in one case, thanks to radium. The invaded lymphatic ganglia were removed and three and one-half years later a new exploration demonstrated the absence of all recurrence.

In cancer of the buccal mucosa, especially in cancer of the tongue, conditions are more unfavorable than in cancer of the skin or of the zones between the skin and mucosa, both from the operative standpoint, as well as that of radiotherapy. With the x-rays alone no cures have been observed; Sticker, however, in cases of papillary cancers of the tongue treated with radium, has had two cures, one of which was persisting after four years. The infiltrating form of lingual cancer is considered the most unfavorable for radium therapy by Sticker. There are good reasons to believe that the local treatment using radium combined with deep roentgentherapy will permit better results.

Cancerous growth of the base of the tongue in a woman of 61, large as a 3 mark piece, extending in the buccal cavity and to the alveolar edge, was treated in this way in August, 1918, in our radiological section by Dr. Jungling and five months after the radiation a complete clinical cure was observed. This woman is still alive today, but unfortunately we have not succeeded in getting her back to Tubingen for an examination.

The complete removal of the tongue is a very bold and dangerous operation. At the price of the serious mutilation which it entails only a slight chance of cure is obtained. Bearing in mind observations such as the preceding in spite of the fact that it has not been put to the test of time, we are, nevertheless, authorized to continue methodical researches on the combined use of radium and x-rays in the treatment of cancer of the tongue.*

For cancer of the jaw, some cases of healing by radium have been reported. But we know particularly through the teachings of our old master who has passed, Franz Kronig, that the resection of the upper jaw has given a notable percentage of healings which have lasted from 10 to 26 years. We know also that the post-operative mortality in resections of the jaw has been favorably lowered by the use of local anesthetic. We know further that the progress of dental prothesis and, for the lower jaw, the secondary bony grafts, remedy functional troubles quite well. We cannot, therefore, decide in a still operable cancer of the jaw to abstain from operative intervention.

In cancer of the pharynx and the larynx the observations of Werner at the Samariterhaus at Heidelberg are particularly worthy of attention. Under the combined action of radium and x-rays, in crossfire, cancer of the pharynx frequently regresses. However, as a rule, distant metastases and more rarely a local recurrence spoil the success attained. The results were more favorable in cancer, histologically determined, located in the part of the larynx above the vocal cords. In borderline cases healing was observed without recurrence in two years. Oedema of the glottis is a danger which must be considered, following the reac-

*The remarkable successes obtained in the treatment of cancer of the tongue by Dr. Regaud (of Paris) and his collaborators, thanks to the gradually perfected method of radium implantation, may well be referred to at this point. (Beclere).

tion produced by intense radiation. Many times a tracheotomy may be necessary. As to cancers of the larynx at the beginning one may cure by the extirpation of half of the organ and we have ourselves seen in a number of cases no response to the x-rays, so that they should still be subjected to surgery.

Cancer of the œsophagus is best treated by a combination of radium and x-rays. Many times in our clinic we have obtained notable and persistent improvements which cannot be too much appreciated in so painful a condition beyond the resources of surgical treatment. Difficulties in deglutition disappear and in one case, six months after the last irradiation with radium and x-rays, œsophagoscopy revealed no neoplastic growth. By the aid of a gastrostomy which, with or without accentuation of the esophageal stenosis becomes more or less rapidly necessary, the introduction of a tube of radium in the esophagus, using the technique of catheterism, is generally facilitated.

For the stomach and intestine, there do not exist at present observations which would oblige us to leave operative methods. Today, as in the past, the operable cases should be operated as soon as possible. If our therapeutic indications may be modified some day, it will be first of all with regard to the rectum, for Chaoul, at the clinic of Sauerbruch, has obtained remarkable improvements, using only x-rays with a special technique.

In this case also our preference has been for the combined treatment. As a general rule, however, it provokes at first considerable tenemus. In five cases of cancer of the rectum which were treated in 1918 in our clinic with a combination of radium and x-rays, 3 have died. But two women, one of 62 and the other of 63 years, are still actually living and in good general health, almost three years after the treatment. The one is active as a housewife. On local examination she experienced no pain and declared to the doctor that she felt so well, apart from a slight incontinance of the sphincter, that she would not wish to be examined further. The second patient had a circular ulcerating cancer, almost immediately above the sphincter. While adherent to the vagina it was still movable and could have been removed but the patient refused operation, and for this reason was irradiated. An examination was made in March, 1921, which showed a completely normal condition and even the sphincter was functioning very well. This is a case of cancer of the rectum with clinical cure without operation for nearly three years, exactly 34 months after the irradiation.

That cancer of the breast may be cured clinically without operation and solely by the use of x-rays may no longer be doubted. However, cases so treated which have persisted for a long time are rare and we have only one single notable statistic, published after his death, by Opitz which includes 62 cases of which 11 or 16.6 per cent. remain without appreciable recurrence for three years. Of 14 women, where the cancer was operable when Kroenig examined them, and who were not operated but rayed, only two or 14.2 per cent. were free from recurrence after three years.

Operation alone without radiotherapy has given at the clinic at Kiel on 118 cases 46 per cent. and at the clinic at Tubingen on 130 cases 38.4 per cent. of cures without recurrence after three years. It is true that these two figures cannot be unreservedly compared with those of Kroenig and Opitz, not only because the latter includes inoperable cases but also because radiotherapy is a treatment which is in course of

development while surgical exeresis constitutes a method whose development is achieved. However, if on 14 operable cases (or even on 17 cases since there were three noted as disappeared which Opitz discarded), only two survived after three years, we must recognize that radiotherapy does not give good results. When cancer of the breast is operable, we therefore are faithful to surgery.

The success of Bumm in causing the regression of a cancer of the cervix of the uterus by raying through the abdominal wall was a step of first importance in the treatment of deep-lying cancers.

Since then there have been employed up to the present three modes of radiotherapy for cancer of the uterus: Treatment by radium alone, as outlined particularly by Doederlein and by Kehrer; treatment solely by x-rays the technique of which was developed by Seitz and Wintz; and then the combined use of both sorts of rays, which is actually the method of treatment by far most used. Remarkable success has been obtained by these three methods and success which has persisted.

However, up to the present this success has not surpassed the statistics of operative success. As a particular advantage of radiotherapy one must count that even inoperable cases have been healed. In any event Seitz himself in his report to the Congress of Gynecologists last year considers the important question of knowing whether cancer of the uterus should be operated or rayed without operation as a question no longer in doubt. So also a whole group of gynecological clinics has remained faithful to operative treatment in all operative cases. But these clinics proclaim without reserve that the operation should be followed by prophylactic irradiation and that this practice has notably reduced the number of recurrences. According to Warnekros it has reduced in the proportion of one in three.

But even if the judgments of the gyneologists were more concordant, and if unanimously in the case of cancer of the uterus, the question was decided in favor of radiotherapy, which it is not, we should not, as surgeons, follow the movement in our domain save with great circumspection, because in cancer of the uterus the conditions in many respects are more favorable for radiotherapy than in other cancers. Up to the present in cases of operable cancer it is only in certain carefully chosen localizations that we would be able to renounce operation in favor of radiotherapy.

Thus, with the exception of cancer of the œsophagus, technically accessible to the knife, but practically inoperable, we will send only to radiotherapy cancers of the skin and cancers of the lip, and under some conditions but not always cancers of the tongue; finally, cancer of the larynx which is located above the vocal cords and perhaps, but with precaution, cancers of the rectum.

It is with the greatest of satisfaction that we recognize unreservedly all that roentgentherapy has done in the inoperable cancers. There is no need for my discussing this at length. You know from your own experience, for example, in cancers of the breast, that fertile source of voluminous neoplasms, solidly adherent to the neighboring tissues. You have seen how the adhesions disappear, the regression of the edema brought about by glandular metastases, how the discharging and ulcerating growths cicatrize. But you know also that these ameliorations but rarely reach a clinical cure even for a time; that in general cancerous residues persist rebellious to the radium rays or there appear, either in

the neighborhood or further away in other points in the organism new metastases.

In all conditions there are exceptions. Thus, for example, the patient with inoperable cancer of the breast was found to be exempt from recurrence during the fourth year after irradiation and this patient died of a fever five years after the beginning of the treatment. But these exceptions do not nullify the rule that even with the aid of radiotherapy the cure of inoperable cancers cannot be obtained.

Inoperable tumors may at times be transformed to operable. In such a case it seems illogical to operate in place of continuing the first treatment. As a support for the complementary operative treatment, this decisive argument may be urged that, in general, the residual tumor ceases to respond to roentgentherapy, and further irradiation has only the result of provoking an x-ray ulcer.

It was thus in a case of inoperable cancer of the lip, firmly adherent to the maxilla and with invasion of the chin, preliminary irradiation followed by excision of the refractory residue gave a full measure of success. For an organ such as the stomach, where Finsterer in the face of an inoperable cancer has methodically adopted this manner of action, we may ask if this is a way by which decisive success may be obtained. It is one which is in need of a more rigorous demonstration.

Post-operative recurrences may often, thanks to raying, disappear for a long time and sometimes may even be definitely suppressed. Twenty-one women operated for cancer of the breast with subsequent inoperable recurrences were treated with success by x-ray by Warnekros, six of them remaining well and without new recurrences during the period of observation, which in 1920 covered four, five and six years. We ourselves have observed in the case of the superior maxilla a demonstrative fact which bears a particularly remarkable lesson. A very extensive case of cancer of the upper jaw with invasion of the orbit was treated by resection of the bone and curetage of the orbital cavity. During the year which followed the operation, there appeared in the depth of this cavity nodules of recurrence, but the x-rays caused their disappearance and the last examination, three and one-half years after the operation, two and one-half years after the disappearance of the recurrence, the patient was in quite satisfactory state of health.

Facts of this sort incline one vigorously to put an obstacle to the development of recurrences after operative treatment and as a result to prevent them by the destruction of the cancerous nests which exist in the tissues. For this reason prophylactic post-operative irradiation is almost generally recommended and particularly used in gynecology. I myself was an enthusiastic partisan for this prophylactic treatment and I was awaiting what the statistics of cancers of the breast radiated after operation would demonstrate as to the value of the method by comparison with cancers operated but not radiated. We were greatly surprised by the results of the work of Neher in our clinic, since they were precisely the contrary of what one might expect. It was that post-operative irradiation of operated cancers gave us a smaller number of definite healings and a greater number of recurrences, and above all a greater number of recurrences in the year following operation. We are thus confronted with questions which are not easy to answer.

In the question of roentgentherapy of sarcoma I will rest on the work of Jungling and will content myself with recalling the report which he has presented at Nauheim to the Congress of German Naturalists:

this report has appeared some weeks ago in Strahlentherapie, volume xii. Here I will limit myself to citing the most important of his practical conclusions, and in the paper cited may be found the detailed reasons which have as their basis the experience acquired in our clinic.

1. Lymphatic sarcomas react perfectly well to irradiation and, bearing in mind the unfavorable results of operation, should be submitted to roentgentherapy. In general, however, this does not prevent the extension of the disease to the neighboring glands nor the appearance of distant metastases. Werner, at Heidelberg, has been able to follow cures extending over more than five years.

2. In the case of periosteal sarcoma at the joint of the limb, shoulder zone, and in the pelvis, the employ of roentgentherapy is recommended, for the results of operative intervention, even radical amputation or disarticulation are here indisputably bad. Sonntag has published a brief observation on the periosteal sarcoma of the humerus in the epiphyseal which was healed for over five years following roentgen treatment.

3. In the treatment of myelogenous giant-celled sarcoma radiation should be used at the time of operation and if there is a question regarding amputation it is preferable to try roentgentherapy.

4. In osteosarcoma of the skull, at the clinic of Tubingen and at other clinics roentgentherapy has given cures of long standing.

5. In sarcoma of the superior maxilla, notable success has not been obtained up to the present with radiotherapy. Now as in the past the operable cases should be treated by resection which gives in a third of the cases a durable healing.

6. In all cases of inoperable sarcoma there is the formal indication for a trial treatment with x-rays.

The value of this recommendation extends even to the gliosarcomas of the brain which the x-rays, passing through the skull bone, may cause to regress temporarily at least at the same time causing the improvement in symptoms of cerebral compression. Roentgentherapy here has the same action as palliative trephination.

The success by radiation in tumors of the hypophysis is very remarkable. There is a series of splendid observations in which troubles with the sight following pressure exerted by the tumor on the chiasm of the optic nerves, such as bitemporal hemienopia or amaurosis, have been improved or even overcome. A patient who was sent to us to be operated, having a progressively rapidly diminishing visual field, was only rayed in our clinic by Jungling using strongly filtered x-rays: the ophthalmological examination was made by Fleischer. A very sharp improvement in the sight actually lasted for three years. The patient, who could neither walk alone nor write, since she could not see what she was writing, read and was able to write to us in good writing a letter of four pages, wherein she assured us that she is able to work and expressed her joy and thanks. According to the report which the ophthalmological clinic sent us a further narrowing of the visual field has not come on. I am mentioning this case since to my knowledge it is the first which has undergone the proof of time for so long a time. While one may not always certainly obtain such success as in the case

just noted operative treatment here meets competition whose value cannot be underestimated.*

Finally it is the same with the sort of tumors which, like tumors of the hypophysis, are on the margin of neoplasms of good and of bad nature, that is the fibrous naso-pharyngeal tumors. I base my conclusions on my very favorable experiences with radiation for saying that one is not authorized to operate these tumors, whose removal always remains dangerous no matter what method is used, whether that of Langenbeck, that of Kocher or of others, if penetrating roentgentherapy has not been tried first.

Successes such as I have reported, which would have seemed unbelievable twenty years ago, have made a great many conversions in spite of the fact that cancer of the rectum has not been controlled for more than 34 months nor the decisive improvement of the tumor of the hypophysis longer than 3 years. As operators we may deplore it, since it will lead to a certain restriction perhaps for operations which are a great honor to our art, but as physicians we must render homage to progress and rejoice in it with our patients.

Justice requires, however, that we do not forget the dangers and inconveniences to which radiotherapy is not exempt. We must recall, briefly as it may be, that besides the earlier roentgen burns which correct dosage permits avoiding, there are also tardy necroses which can be seen occurring months and even years afterwards. These facts merit attention no less than the general disturbance which results from a prolonged reaction of deep roentgentherapy, and which may reach from the simple roentgenkater to the incurable cachexia, the roentgen cachexia. Fortunately these complications are observed only rarely and for this reason are not a heavy weight in the balance. But there is an inconvenience of more general importance: the uncertainty of success which I have already mentioned several times in my explanations. Does this rest, as Seitz and Wintz believe, on faults of technique, and may we hope to overcome them?

This leads to the second capital question. Is the task of roentgentherapy solely to give to all parts of the body which harbor cancerous cells a determined dose, the lethal dose, for these cancerous cells? When we succeed in accomplishing this task, may we be really certain of success? In other words, is there a cancer dose?

This question is closely connected with the following. Do the cells of all cancers in different patients in different parts of the body and showing the different histological forms react essentially in the same way to roentgen rays, or is this not the case? Here is what Seitz and Wintz say: "According to our experience, the observed variations in the radiosensibility of the cells of malignant tumors are not very great. They vary almost within the limits which we have found in studying the reaction of the skin. We ought, therefore, to refuse to admit a refractory state of sarcoma cells or of carcinoma to the roentgen rays." On the other hand, here is what observation has established: On the one side, there are cancers, for example the cutaneous metastases of breast, cancers which melt away rapidly under a dose of rays which at most would produce a little erythema in the skin; on the other hand,

*In February, 1909, I communicated to the Medical Society of the Paris Hospitals a new technique for the treatment of tumors of the hypophysis, that of radiations by the fronto-temporal way, as well as observations of a patient treated by this method with remarkable success I have learned recently of a persistence, after nearly 13 years of all of the results obtained by the treatment. A. Beclere.

there are some even among non-cachectic patients which do not regress under a radiation which is lethal for the cells of the normal skin. Our experience agrees perfectly with that of Werner and we can almost without reserve join him in the position which he has taken on this question of radiotherapy as a result of his important observations at the Samariterhaus at Heidelberg. Also Kehrer, Opitz and others have made analogous observations.

To speak of a cancer dose as Jungling has explained it, could have only one meaning, that is that there exists a minimum dose for cancer which one must necessarily attain if there is to be any chance of obtaining a regression of the cancer by radiation. In this restrained sense the concept of a cancer dose is a useful one. But there does not exist unfortunately a cancer dose understood in a sense that such a dose will certainly produce the regression of a cancer; it does not exist even if one is careful to exclude from the argument cachectic patients.

The differences in radiosensibility between sarcomas are even greater. Lymphosarcomas respond to a fraction of the unit skin dose, whereas sarcomas of the upper maxilla, for example, and most frequently melanosarcomas cannot be influenced in a decisive manner by a high multiple of the unit skin dose. The fixing of a single sarcoma dose is impossible. Even more than for the carcinomas, the roentgentherapy of sarcomas becomes in each particular case a trial whose success cannot be predicted except with more or less uncertainty.

The different reaction of malignant tumors to the x-rays and radium rays does not always find a sufficient explanation in the variations of their histological forms. It frequently happens that we find tumors of the same histological structure reacting quite differently to the rays.

Furthermore, it is undoubted that different cells in the interior of the same carcinoma or the same sarcoma show very different sensitiveness to the x-rays. As I observed in 1903 in my researches on the influence of the x-rays on the cell divisions of the eggs of intestinal worms of the horse, and as Kroenig and Friedrich later described according to their experience on tadpoles, the same irradiation under the same conditions will not produce the same action on all individuals, injuring some more seriously than others. In the same way, there exist in a tumor more resistant cells which may escape the effects of the radiation. These resistant cells form a group whose survival lets us understand how unfortunately and too often in a neoplasm which has almost entirely disappeared, there remains a remnant which later radiations can no longer modify.

Does this selection of most resistant cells suffice to explain everything? Can there not also be another sort of immunity, an acquired radio-immunity? In any event, we may practically attribute a number of recurrences to this refractory state. It seems established that one should try to obtain the object by a global irradiation at a single sitting. Since 1903 the best successes which I have seen, have been obtained by a single treatment with high dosage. Kroenig has demonstrated the feebler action of fractional dosage, and Werner, Rapp, Opitz and others following them have pleaded in favor of raying at a single seance. As we see it, apart from the division of the dose, it is always necessary to take into account in every case all the biological conditions, the radiotherapy of malignant tumors is not a purely physical problem.

This proposition holds its value in the last question which I do not know how to pass by . On what point do the x-rays exert their action?

How may one represent the mechanism of their action? To what practical deductions will this view lead?

That the x-rays act principally on tumor cells to damage them, we know from a series of facts to which we do not need to refer. The histological examination of rayed cancers shows the phenomena of cellular degeneration whose nature and intensity are such as are never observed following an inflammation of neighboring tissues. In cancer of the skin treated with x-ray and particularly in the papilla, there is found a very accentuated degeneration of the epithelial cells, which contrasts with the insignificance of inflammatory reaction of the conjunctive tissue of the derma. Furthermore, we have been able to demonstrate with certainty a destructive action of the radium and x-rays on the nucleus of cells in mitosis, and this damage to the nucleus is not suspected of depending on a modification of the nourishing vessels, since it has been observed on eggs at the period of segmentation. This difficulty in the formation of cells, recognized histologically, translates from the standpoint of biology in both the animal and vegetable kingdoms, to an arrest in the process of growth. After all of this we cannot put in doubt that the x-rays have a directly damaging effect on neoplastic cells in process of division.

In addition to this destroying of the vitality, may there also exist an action which augments cellular energy, an exciting action? We must admit indeed that it is a duty to say that the basis of clinical and experimental observations, upon which this opinion rests is neither as large nor as sure as would be desirable in a question of such importance. What comes from the experimental and clinical researches and what we may recognize with certainty is that an excitation or exhilaration in the cell division only comes into play with minimal doses, with truly homeopathic doses. As soon as the radiation dosage is very slightly increased, the neutral line is passed, beyond which the exciting action is transformed into an action which depresses the cell vitality, finally becoming lethal. The damaging action which is the consequence of all strong irradiations without doubt affects the neoplastic cells more severely than normal cells in the vicinity.

It is a matter relatively of a selective action. The selective action of the x-rays was shown with good evidence in the discovery due to Albers-Schonberg of the influence on seminal cells and by the fundamental researches of Heinecke on the rapid destruction of the white corpuscles of the blood by x-rays. As regards neoplastic cells this relatively selective action has been established by such a number of macroscopic and microscopic observations that it is difficult to understand how anyone can doubt this fact, which is one of the scientific priniples of our treatment by means of rays.

However, this affecting the vitality of neoplastic cells does not alone explain all of the facts observed in roentgentherapy of malignant tumors. If it were only a question of killing the cancerous cells, the disappearance of the growth should be more certain the stronger the irradiation and more particularly if all of the parts of neoplastic tissue were to receive a lethal dose. But as a general rule this is never the case.

As an example I may cite a patient in whom, after excision of a cancer of the breast, recurrent cutaneous nodules were suppressed by roentgentherapy. After the last irradiation over one localized area with a filter of zinc and a dose of 100 to 110 per cent. of the unit skin dose,

the remaining nodules ceased to regress. One of these was removed for microscopic examination. At the point of this excision, after a union by first intention, there developed a roentgen ulcer and in the radiated region appeared some new nodules, whereas in the neighborhood of this region nothing of this sort developed. Thus growth of cancerous cells was limited to the region intensely rayed whereas in the surrounding tissue, which had been covered with lead, other cancer cells unquestionably present persisted in their state of latency. It is not a question of a simple excitant action on cancerous cells, since the raying was too intense to the point of producing an x-ray burn.

Cases of this sort show that the defense reactions of the normal tissues against the growth of the cancer are destroyed by irradiation. Such observations, to my mind, lead to the view held by Kroenig, by Theilhaber, by Stephan and particularly by Opitz, that in roentgentherapy of cancer, two factors play a part, on the one side damage produced in the cancerous tissues, and on the other hand the active assistance of the neighboring healthy tissue, which has more to do than to fulfill the part of grave-digger for the dead cancer cells. In radiotherapy of malignant tumors, does the normal tissue which surrounds them undergo a useful stimulation through the action of the x-rays, an action which strengthens it in its fight against the cancer, as Bier has suggested in a general manner concerning the non-operative treatment for tumors, and as Theilhaber, Stephan and Frankel have suggested, particularly for the action of the x-rays? Or is it a matter of the normal tissue, spared by the radiation, conserving its own power of defense? This is a point which has not yet been decided. But in any event we should agree with the advice of Opitz that we must take into account the power of defense of normal tissues and have a care not to overdose them. An excess dose in radiotherapy may do as much damage as too little dosage. The overdose, like the exciting dose, although by different mechanism, may provoke the growth of the cancer .

We must not accord less importance to the general resistance of the whole organism than to the local resistance of normal tissues near the tumor cells. When the power of defense of the organism is lessened by too intense or too extended radiation, or when there develops what Kroenig has called a roentgen cachexia, we see springing up on the ground conquered by the treatment an astonishing neoplastic growth, a manifest proof that in roentgentherapy it is of the highest importance not to neglect the condition of the organism as a whole.

In the process of healing which we bring into play by the aid of the x-rays, we have perhaps the right to view the intricate and mutual actions of different factors: neoplastic cells, neighboring tissues, the defensive powers of the whole organism. This interaction reminds us of the phenomena observed after the experimental grafting of tumors and particularly the processes of healing often set up for cancer of the skin and even cancer of the stomach, as well as in sarcomas. Here, as in those cases, we see a reciprocal action of the mentioned factors. It is true that the tendency to spontaneous healing rarely rises above an imperfect effort. It is only with the additional help of the x-rays that this tendency takes its full value. If such a viewpoint is proper, roentgentherapy is, speaking in a large way, only an increase in the natural processes of healing.

A great number of biological problems are included in the roentgentherapy of malignant tumors. To seek the solutions we must work hard.

DISTURBANCES IN MAMMALIAN DEVELOPMENT PRODUCED BY RADIUM EMANATION *

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The effect of radium on animal development has been the subject of several researches since the early work of Bohn (1), in 1903, upon the ova and larvæ of the sea-urchin. Experiments on developing nematodes, molluscs, amphibians, fishes, and birds are associated with the names of Perthes (2), P .Hertwig (3), Schaper (4), O. Hertwig (5), and G. Hertwig (6). These investigators report developmental retardations following radiation of the ova and developing embryos. They found a particular susceptibility of the nuclei of the cells and a general slowing up in the developmental processes, especially in the case of the central nervous system. The total disturbances, depending upon the period of development when the radiation was applied, resulted in the formation of monstrosities conforming more or less to a general type.†

Similar experiments concerning the effects of x-rays on development have been conducted by many investigators. After exposure to x-radiation, Perthes (7) noted abnormal cell division and a retardation in the development of the ova of Ascaris megalocephala. Gilman and Baetjer (8), after radiating the ova of Amblystoma, and Baldwin (9), the fertilized ova of frogs, were able to produce a fairly constant type of development defect. Injurious results have followed in all cases where mammals have been exposed to x-radiation. It has been shown that when any particular part of a young animal is exposed to a sufficient amount of radiation, that part fails to reach its normal size and is unable to exercise a full degree of function.

Arrests in development and the production of abnormal types may be induced not only by radio-activity, but by many physical or chemical agents. Abnormal temperature changes, treatment by many chemicals, lack of oxygen supply, or the overabundance of carbon dioxide, etc., have produced marked changes in the developing embryo.

The present experiments are mainly concerned with disturbances in mammalian development, before and after birth, as a result of exposing the embryos of rats, at various times during the prenatal period, to irradiation from radium emanation. The effect on the embryos following radiation of the mother at varying intervals before mating was also determined. These experiments were designed not only to study the factors underlying the production of abnormal types, but through an

*Reprinted by permission from the American Journal of Anatomy, xxx, 133-161, Jan. 1922.

†In connection with the above statement, and applying to x-ray treatments as well, the question of dosage is an important one. A survey of the literature shows that there was a very wide range in the severity of the dose employed, and in several cases the experimental settings were inadequately described (Bohn used 'some centigrams' of pure radium bromide for from twenty minutes to two hours). The amount of radium metal used in the investigations that have been mentioned varied from 2 mg. to 35.1 mg., and the time from a few seconds to several hours. The deleterious changes in the animal tissues varied with the amount of radium and the time of exposure.

examination of the abnormal to gain a clearer insight into the nature of normal development and differentiation.§

I acknowledge with pleasure my indebtedness to Dr. James Ewing for his aid in the interpretation of the pathological results.

METHODS AND APPARATUS

Two methods were used for applying the radium emanation. In the first method an 'active deposit' was obtained by exposing a definite quantity of common salt to a comparatively large amount of radium emanation, about 500 millicuries were used, or the amount of radium emanation initially equivalent to one-half a gram of radium metal. To the radio-active salt thus produced sufficient water was added to make a physiological solution. The pregnant rats were injected subcutaneously in the shoulder region and intravenously through the caudal vein; 3 to 4 minims constituted the usual dose. Because of the rapid loss of radio-activity of these solutions, the injections were made immediately after the preparation. The details involved in preparing and measuring the doses, as well as the methods for protecting the experimenter, are described elsewhere (10 and 11). The activated solution exhibited all the known phenomena of radium metal itself; alpha, beta, and gamma rays were present, but the greatest physiological effects were probably due to alpha-ray activity. After long experimentation, a dose of 5 millicuries was found to be the maximum applicable to the aims of this experiment. In the second method gamma-ray radiation was applied through the ventral body wall of pregnant rats at nearly full term. A large amount of radium emanation was used, an amount equivalent to 1½ grams of radium metal, filtered by 2 mm. of lead and ½ mm. of silver. The source of emanation was 1 cm. away from the animal. The applicator, called a 'lead tray' in clinical usage, was 6 cm. in diameter and 1.5 cm. high. This was placed in the bottom of a small wire cage, 10 by 13 cm. in diameter and 10 cm. high, and was covered by a thin sheet of cardboard. The animal was placed on this paper immediately above the applicator.

Preliminary tests showed that a dose of about 1300 millicurie hours was sufficient to produce developmental arrests in the embryos without killing the pregnant animals. Doses as high as 2900 mc. hrs., however, were successfully used in some cases. The embryos were killed by ether, and histological material procured at various periods after the treatment. The tissues were fixed in Bouin's solution, cut in serial section, and stained with haematoxylin and eosin.

EXPERIMENTAL RESULTS

Series A. Injections of Radio-Active Solutions.

1. *Subcutaneous Injections After Mating.* Sixty-five full-grown, normal, pregnant rats were treated in this series. They were divided into four groups, each treated at different periods after mating. Ten pregnant females were injected 7 days after mating; twenty-four, 10 to 14 days after; twenty-one, 15 to 17 days after; and ten, 18 to 21 days after mating. Many of the animals were killed at weekly intervals after treatment, although some were allowed to reach full term.

Various degrees of developmental disturbances were noted, as shown in the following groups:

§Dr. J. F. Gudernatsch was a co-investigator with the writer during the year 1919. A preliminary report of the work done with him at that time is given in the Proceedings of the Society for Experimental Biology and Medicine, 1920, vol. 17, p. 183.

1. There was a large number of cases where no embryos developed, in others many began development, but were absorbed or aborted at an early time. The females in which no embryos were found, although they were definitely considered pregnant before treatment, occurred among cases treated soon after mating and in those instances where females were autopsied a considerable time after treatment. Figure 1 shows the remnants of maternal and embryonic structures; from the size of the placentae one can see that the foetuses had reached a fair degree of development before the radiation retarded the normal physiological processes. In one case (fig. 2) a small ovoid sac was found attached to the uterine wall by a thin stalk. This apparently represented the remnants of a former embryo and placenta. Extravasated blood and cell detritus were found in this sac and a great many large cells of an epithelioid nature that probably belonged to the former embryonic syncytium. The wall of this cyst was formed by fibrous connective tissue.

2. Embryos were killed by the treatment, but were removed from the mother and preserved before they were absorbed. These showed various extravasations from the vessels of the subcutaneous connective tissue, within the meningeal sinuses, and mainly along the dorsal midline of the body. Figure 3 shows a typical example of such a lesion which was situated in the mid-dorsal line. The mother of this embryo, No. 1167, was mated on April 22, 1919, injected with 4.9 millicuries on May 7th, and was killed two days later. When the embryo was cut in serial section, it showed that the haematoma in the dorsal subcutaneous tissues had exerted sufficient pressure upon the spinal column to produce at one place a complete dislocation. Microscopical examination of the viscera showed no pathological changes. Not all the foetuses of a litter were affected in the same degree. In one case seven foetuses were found, three showing haemorrhagic lesions, two beginning to macerate, and two in the progess of absorption. This variation in resistance was due either to the higher or lower vitality of the embryos themselves or to the amount of radioactivity which passed the placentae. In another case the foetuses, although injured, were carried to full term, and among a litter of six young, two were apparently normal and four showed haemorrhagic spots on the head, face, and along the dorsal midline of the body.

3. Several young of a single litter showed areas of extravasation and were born alive. Their mother died, however, and foster mothers refused to nurse them.

4. Eight litters gave normal living young. This number is low, because, as previously stated, many pregnant rats were killed by the experimenter at various intervals after treatment. The average number of young per litter was 4.8, as compared with 6.5 per litter for the control rats, but the probable errors indicate that this difference is, very likely, not significant. Only one litter, containing four young, survived a treatment given seven days after mating. Several of the rats of this group, which had apparently escaped the full radium exposure during the uterine period or perhaps they were more resistant to it, when mated inter se produced litters of apparently normal young of normal fertility. The offspring of these animals, about twenty in number, were observed for two generations, but no abnormalities were noted.

II. *Subcutaneous Injections Before Mating.* Seventy-seven females were treated in this group, eleven died as a result of the injec-

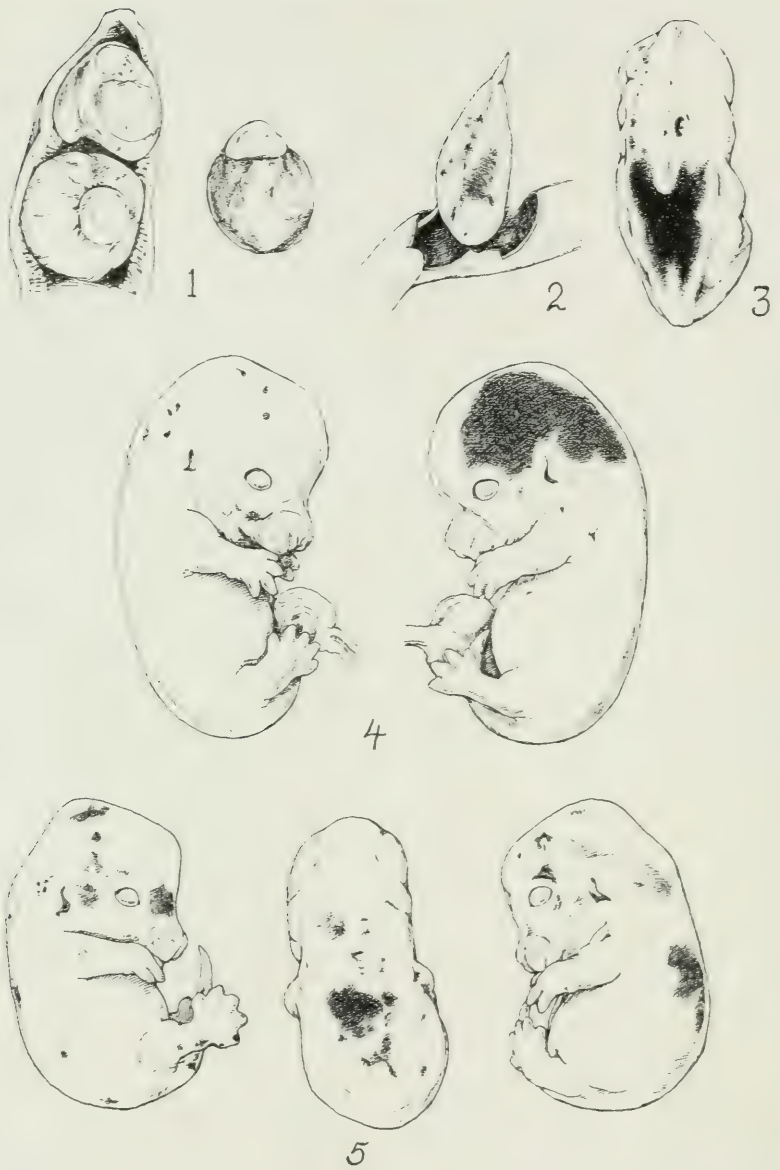

Fig. 1. Two well-developed placentae are shown at the left attached to a uterus which has been partly opened. The remnants of embryonic tissue are superimposed on the placentae. At the right is a placenta which has been dissected from the uterus, and shows more clearly the remains of embryonic material, here represented as a lighter area in the upper portion of the drawing. Female mated April 22, 1919, injected May 7th, killed May 6th. Dose = 4.6 mc. (subcutaneous).

Fig. 2. A stalked sac partly dissected from the uterus, showing the remnants of a former embryo and placenta. Female mated April 22nd, injected May 7th, killed May 16th. Dose = 4.8 mc. (subcutaneous).

Fig. 3. This is a dorsal view of a rat embryo, showing a characteristic area of extravasation due to the treatment of the mother during pregnancy. Female mated April 22nd, injected May 7th, killed May 9th, at which time

tion before they were mated, while several were killed at weekly intervals after mating, and some were allowed to continue to full term. Thirty-four animals were injected between 5 and 7 days before mating; seventeen, 10 to 14 days before, and fifteen, 20 days before mating.

Only three litters in this group showed abnormal young. The most interesting was a litter of seven, in which case the female was treated with 4.2 mc., 22 days previous to fertilization, and the foetuses, approximately 16 days old, showed very pronounced areas of extravasation, which in one case (fig. 4) covered a large area on one side of the head and a few small scattered areas on the other side. These areas were not only along the dorsal midline, but also on the lateral surfaces of the body as well (fig. 5). The lesions were much more widely distributed and more variable in size than in the cases recorded under Section I. Although the conditions that produced these results were repeated many times, the above is the only case where positive data were obtained. Usually the female had either been rendered sterile or the young were killed and absorbed during early stages. There were two other cases, however, where young were found with haemorrhagic areas, and these occurred in a group of females that were treated seven days before mating. Female 85 was given a dose of 6.6 mc. on November 7, 1919. It was mated on November 14th, and as three young were born December 11th, fertilization took place about fourteen days after the treatment. Two of the young were apparently normal, but one showed a large haemorrhagic area, which involved most of the right side of the snout, the right eye, and a portion of the lower jaw on that side. This area disappeared after three days. Female 99, injected and mated at the same time with female No. 85, received a dose of 5.6 mc. Five young, three males and two females, were born on December 13th, making the date of fertilization about sixteen days after treatment. One male and one female showed definite haemorrhagic areas on the face. Consideration of these cases will be deferred until later.

Seventeen females following treatment were killed at varying intervals after mating and showed markedly haemorrhagic or cystic ovaries and congested uteri. In these cases radium emanation apparently had either so altered the maternal tissues as to prevent fertilization or development when started was soon followed by the death of the embryo and its absorption. Many nodules were found in the uteri in which it was impossible to differentiate between embryonic and maternal structures.

The remaining females (as previously stated, eleven died between the period of treatment and mating) produced either full-term normal young or young apparently normal at autopsy. Several of these living

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seven foetuses were found about fifteen days in development. Two of the litter were macerated and two absorbed. Dose = 4.9 mc. (subcutaneous).

Fig. 4. Areas of extravasation are shown in the two views of this embryo, similar to the condition shown in figure 3, but in this case resulting from treating the mother twenty-two days before fertilization. There are a few small scattered areas over the right side of the head and a large area of extravasation on the left side. Female injected April 22nd, mated May 12th, killed May 30th. Seven foetuses were found, fifteen to sixteen days old. Dose = 4.2 mc. (subcutaneous).

Fig. 5. These are three views of another foetus, a litter mate of the one shown in figure 4, showing the wide distribution of the extravasated areas over both sides and back of the animal. The experimental conditions are the same as for figure 4.

young grew normally and were mated inter se, but produced no abnormal offspring, although observed for two generations.

III. *Intravenous Injections After Mating.* The intravenous injections were primarily planned to act as a check on the series of subcutaneous treatments. The object was to determine the immediate reactions that might occur in the embryo as a result of injecting a comparatively large dose of radio-active solution into the circulation of the pregnant female, and whether these reactions would be similar to those already recorded for the subcutaneous series. The toxic reactions were so prompt and fatal that it was not necessary to treat many animals to settle this point. A typical case in that of female No. 123. This animal, of about nineteen days' pregnancy, was treated with 30 mc. injected directly into the blood stream through the caudal vein. This was six times greater than the usual dose in the first two series. Three young were born dead twenty-four hours later. They showed very definite radium changes, typical of those already recorded for the subcutaneous series. Figure 6 shows a foetus still attached to an apparently normal placenta, but a characteristic area of extravasation was found over a considerable portion of the left side of the head. In figure 7A a dorsal view shows another embryo with two comparatively small haemorrhagic areas along the dorsal midline, and the placenta in this case is also normal. The third foetus in this litter was apparently normal, but the placenta (fig. 7B) had acted in the nature of a 'shock absorber' in protecting the foetus from exposure to the radio-activity, and it was so swollen and completely filled with blood as a result of its injury, that it had the appearance of a large haemorrhagic sac.

Series B. Results from Radiating Nearly Full-Term Pregnant Rats With Gamma-Ray Radiation.

Ten rats were treated at the end of about nineteen days of pregnancy. It was found that exposure to about 1350 mc. hrs. of radium emanation was sufficient to produce very decided changes in the embryo and yet leave the pregnant females sufficiently uninjured to be able to nurse their young and care for them until after the weaning period. When the dose was increased to 3378 mc. hrs., the young were severely injured, and were either killed outright or died two or three days after birth.

The following are the conditions that resulted in the first generation of animals treated in utero with a dose of about 1350 mc. hrs.:

1. The young of each litter were born two or three days after the treatment, alive and apparently normal.

2. About ten days after treatment, about half of each litter became markedly anemic, showed symptoms of diffuse edema, and promptly died. There was an easily recognizable slow development of meningeal and spinal-cord haemorrhages, similar to those already described as a result of treatment by radio-active solutions. A series of these lesions is shown in figures 8, 9 and 10. Figure 8 shows a young rat with the dorsal integument partly dissected away, exposing a typical haemorrhagic area in the region of the frontal lobes. The slow development of this lesion could be easily noted through the thin, transparent scalp. This young was one of several treated in utero with 1350 mc. hrs. of gamma-ray radiation on February 21, 1920. It was born two days later, and died on March 3rd. The young rat shown in figure 9 was a litter mate of the previous animal. It shows the presence of three distinct haemor-

rhagic areas, a small frontal lesion, a fairly extensive one in the occipital region, and a small lesion in the subcutaneous tissues in the thoracic region, near the middorsal line on the left side of the body. This animal also died on March 3rd. A third animal belonging to the same litter is shown in figure 10. Here is seen a still more acute reaction, as shown by the fact that the animal died a day sooner than in the two cases above. There is an extensive area of meningeal haemorrhage which covers most of the dorsal portion of the brain, involving the frontal and occipital regions and the medial area between, as well as a considerable portion of the right temporal area. In addition, a distinct, rounded haemorrhagic lesion may be noted on the reflected skin on the left side of the body. This lesion occurred in the midshoulder region of the back.

The heads of several of the young rats showed marked lateral compression. In one case a haemorrhage so affected the spinal cord as to produce complete paraplegia. The tissues of these animals were studied histologically. Save for the mechanical disturbances produced by the presence of the extravasated areas, the most marked pathological conditions were seen in the liver and intestines. In the first case there was a pronounced fatty degeneration of the hepatic cells, and in the second, a desquamation of the lining cells of the intestinal mucosa.

3. It is interesting to note that the other half of each litter survived the treatment, grew to a normal size, and some animals have lived for over eighteen months. They showed the effects of the late uterine treatment by the following arrests in development:

a. The first pathological condition noted was that the eyes became smaller, the pupils opaque, and there finally was a complete, or nearly complete, closing of the lids and total blindness. This condition was first observed a short time after the eyes had opened. The photographs in figure 11 show three views of a female rat about one year old with typical eye deformities. The upper view shows the entire animal, which had grown to normal size and weight for its age. The left eye was nearly completely closed, as is shown more clearly in the lower right-hand view of the head at a higher magnification. Both pupils were opaque, but, as shown in the illustration, the right eyelids were slightly more opened than those of the other side. The animal was one of a litter treated in utero on March 8, 1920, was born six days later, and the photograph was taken on March 1, 1921. The dose in this case was 2920 mc. hrs. of gamma-ray radiation, which was a dose higher than that usually tolerated.

b. Mating tests showed that both the males and females were completely sterile in the first lots, but subsequently a first-generation female, that had been treated with 1350 mc. hrs., mated with a male similarly treated, gave birth to nine apparently normal young.

c. Before these adult offspring of treated animals were killed for histological examination, their neurological reactions were very carefully studied. The animals, being blind, when startled assumed various defensive attitudes, but save for these reactions their behavior was remarkably normal. There was no ataxia in locomotion or in any of the feeding reactions, auditory acuity was normal, and there was no cutaneous hypoesthesia or other sensory disturbances. Except for blindness, there was nothing to suggest abnormal sensory function.

d. When these animals were autopsied, marked developmental disturbances were noted in the condition of the central nervous system.

Fig. 6. There is a large and a small area of extravasation on the head of this foetus. The mother was injected intravenously with 30 mc. of radioactive solution and three young, about full term, were born twenty-four hours later. All were dead. In this case the attached placenta is apparently normal.

Fig. 7. The lower figure (A) shows an embryo with two dorsal head lesions and an apparently normal placenta. This is a litter mate of the animal shown in figure 6. At B is indicated a large haemorrhagic placenta from the third young of this litter, which itself was apparently normal.

Fig. 8. Dorsal view of a young rat with the skin dissected to either side. There is a prominent area of meningeal extravasation in the frontal region. This animal was treated in utero with 1350 mc. hrs. of gamma-ray radiation on February 21st and was born apparently normal on February 23rd. It died on March 3rd.

Fig. 9. Dorsal view of a young rat showing areas of frontal and occipital extravasations which were within the meningeal sinuses. There is a smaller lesion in the left dorsal thoracic region. This is a litter mate of the animal shown in figure 8, and the experimental conditions were identical. Death occurred on March 3rd.

Fig. 10. There is an extensive meningeal extravasation over a considerable portion of the hemispheres, and a haemorrhagic lesion is shown on the reflected skin from the dorsal interscapular region. This is a litter mate of the animals shown in the two preceding figures. Death occurred on March 2nd.

The cerebral hemispheres were greatly reduced in size, and in several cases very little cortical material remained. Those portions of the brain that were ontogenetically older (the archiostriatum and the cerebellum) were apparently normal. The optic tracts were markedly atrophic. Correlated with this disturbance in brain development, the skull was found to be asymmetrical, narrow, thicker than normal, and concave in the frontal region.

Figure 12 shows a dorsal view of a normal, untreated brain of an adult rat, magnified five diameters. In figures 13 and 14 are dorsal and lateral views of a brain of one of the rats which belonged to the same litter as those of section 2 of this series. This animal was treated with 1350 mc. hrs. on February 21, 1920, was born on February 23rd, and was killed December 31, 1920. This was one of the animals which (except for blindness) showed no abnormal neurological reactions. The magnification in figures 13 and 14 is the same as that for the control brain in figure 12. The dorsal view in figure 13 shows an apparently normal cerebellum and normal olfactory lobes, but the part of the brain which represents the rudiments of the hemispheres shows a great lack of development of cortical substance. In a side view of the brain in figure 14, the cortex may be seen to be very thin; indeed, not completely covering what should normally be the frontal, occipital, and lateral aspects of the brain. The remains of the hemispheres do not sufficiently approach each other in the median line to cover the colliculi beneath. In figure 13 the meninges on the left side of the brain have been removed, but on the other side they have been left in place. It was possible in this specimen to see the lateral ventricles through the transparent membranes. Several other brains have been studied which showed various degrees of developmental arrests resulting from radium treatment. In some cases the hemispheres were markedly reduced in size, were widely divergent in the median line, and yet the pallium was complete over the entire surface. In all these cases there was marked optic atrophy. These brains are now being sectioned, and a study of them in greater detail will be the subject of a separate communication.

e. A histological study of the eye showed that the eyeball was reduced to one-fourth the normal diameter. The retina was missing, but traces of the choroid remained as a few scattered pigment cells. The cornea was three times as thick as normal and covered with four or five layers of opaque squamous epithelium. The optic nerve was extremely small, not more than one-third the normal dimensions.

f. The testes of the radiated animals were decidedly atrophic, and a comparison with the normal is shown in the photograph in figure 15. The diameters of the testicle alone (minus the epididymis) of the experimental animal was 14 mm. for the length and 7 mm. for the width, while the control measurements from normal animals of the same age and weight and with the same method of fixation were 21 mm. for the length and 11.5 mm. for the width. The epididymis of the radiated testis was practically missing. A small portion of the tail remained, but the head and body of the epididymis had failed to develop. Histological examination shows that there is little evidence of spermatogenesis. Some tubules seem to contain imperfect spermatoblasts and forming spermatozoa, but the great majority of tubules show complete degeneration and loss of epithelial cells, and contain loose granular material, which in places is calcified. Some spermatic tubules are greatly dilated and filled with granular material. Very few interstitial cells are visible.

The ovary of the radiated animals was reduced to one-fourth or one-fifth the normal size. The graffian follicles were entirely missing. Groups of lutein cells persisted in small numbers, but showed marked hydropic degeneration. Some of the large vessels about the ovary were sclerosed.

g. The liver, kidney, lungs, spleen, and the other organs were examined, but showed no pathological disturbance.

CONTROL GROUP

Pregnant rats of the same stock, the same age and weight, were injected subcutaneously and intravenously with equal amounts of solutions that previously had been strongly radioactive, but were allowed to 'decay,' until they had lost their radio-activity. These experiments gave absolutely negative results. As a control to the gamma-ray experiments, pregnant rats, sisters of the treated animals, were allowed to breed under exactly the same experimental conditions. No abnormal young were observed.

DISCUSSION AND SUMMARY OF RESULTS

It has been shown that when doses of radio-active solutions are injected into an animal marked physiological reactions take place. Large doses produce severe toxemia, resulting in pronounced pathological changes in the various viscera of the white rat (10). A study of metabolic changes in dogs, as determined by urine analysis, showed that, following intravenous injections of such solutions, there were very decided increases in the total nitrogen content of the urine, the urea, creatinine, uric acid, and the total phosphates (12). A prompt reduction occurred in the number of white blood cells of the dog after intravenous injections of these solutions, associated with a marked decrease in the relative percentage of circulating lymphocytes (13). In order to reduce as much as possible the severity of the reaction, very small doses of radio-activity were used in the experiments recorded in this article. But even with comparatively small doses, certain rats treated in utero showed very acute reactions. Many were killed by the treatment and and were absorbed or aborted. Others were found showing pronounced areas of subcutaneous extravasations, mainly situated along the mid-dorsal line of the body and within the meningeal sinuses. This condition was probably due to the destructive action of radium on the endothelium of the blood vessels, as well as a possible increase in blood pressure, as was shown to occur in the dog by Burton-Opitz and Meyer (14) after intravenous injections of very small quantities of radium bromide. A similar reaction of the blood vessels to radiation was previously reported by Halkin (15) for the skin of pigs, and by Danysz (16) for radiated mice. This destructive action of radium on the blood vessels is in line with clinical observations on the usual prompt regression of very vascular tumors (the angiomata, in particular) after exposure to irradiation.

The changes in the rat embryos of this experiment are interesting in so far as they show that a sufficient amount of radio-activity was able to pass the placenta and subsequently affect the developing embryo. This occurred after subcutaneous as well as intravenous injections of the mother. By far the most interesting observation concerned the presence of lesions similar to those described above in rat embryos whose mother was treated with radio-active solutions a considerable time before mating.

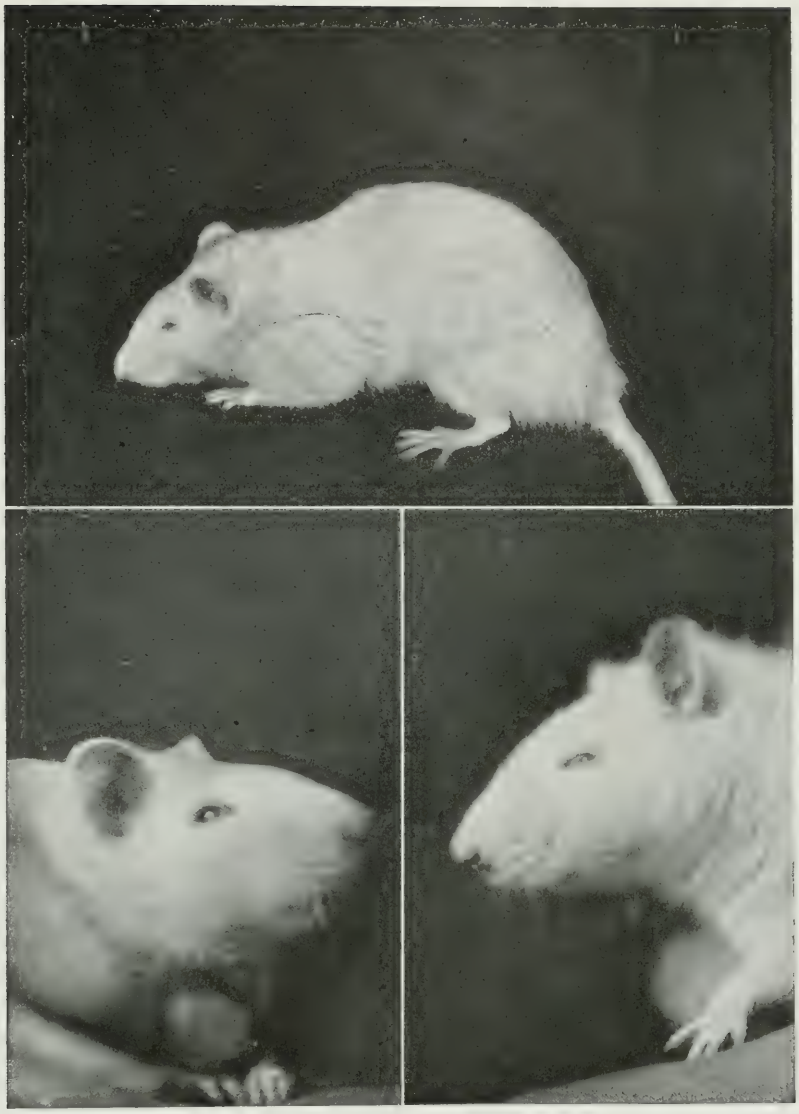

Fig. 11. The upper photograph shows an adult rat with eye deformities due to gamma-ray irradiation during the prenatal period. The size and weight are normal for its age. The lower figures show the lateral views of the head at a higher magnification. Both pupils are opaque and the left eyelids are nearly completely closed. Mother treated on March 8, 1920, young were born on March 14th, and photograph was taken on March 1, 1921. Dose = 2920 mc. hrs.

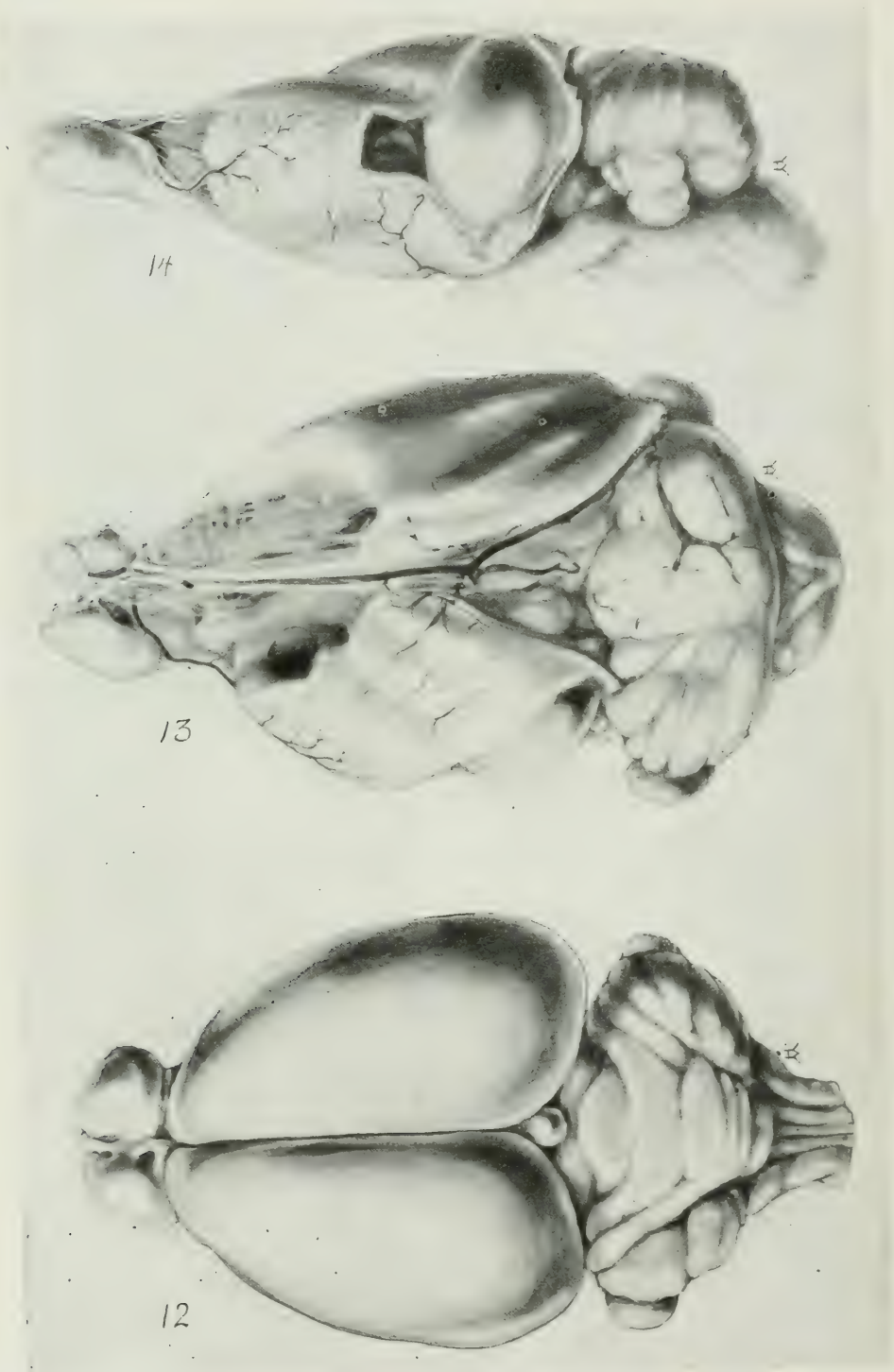

Fig. 12. Dorsal view of a normal untreated brain of an adult rat.
Fig. 13. Dorsal view of the brain of an adult rat showing the marked devel-

mental arrest in the formation of the neopallium. The meninges on the left side of the brain are removed. Mother treated with gamma-ray irradiation on February 21, 1920, young were born on February 23rd. Brain from radiated young removed on December 31, 1920. Dose = 1350 mc. hrs. (For further reference see text). The magnification is the same as for the drawing of the normal brain.

Fig. 14. A lateral view of the brain shown in Fig. 13. This shows the thinness of the remains of the cerebral cortex and its total absence in the frontal and occipital regions. (For further reference see text).

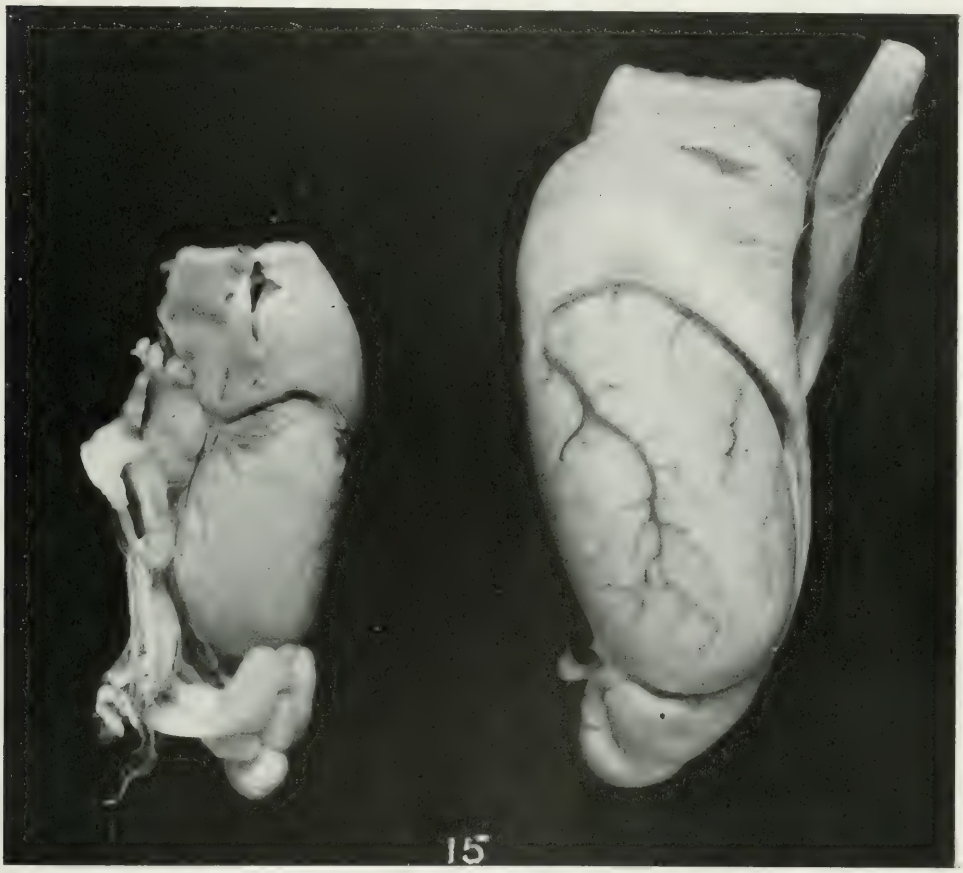

Fig. 15. At the right is shown a normal untreated testicle of a white rat surmounted by a well-developed epididymis, which is partly obscured by fat. At the left is a radiated testis showing considerable atrophy. The single small lobe at the very bottom of the photograph represents the remains of the tail of the epididymis, the head and body of that part being completely missing. The animal was treated in utero on February 21, 1920, was born February 23rd, and was killed December 31, 1920. Dose = 1350 mc. hrs. of gamma-ray irradiation.

The writer has no explanation to account for this phenomenon. It would appear that the treatment of the mother several days previous to conception has lessened the faculty of the later-developing embryo to form proper endothelium of the blood vessels, and the wide distribution of these lesions over the body of the embryo (peculiar to this group of animals) would tend to substantiate this view. One female was injected twenty-two days before fertilization, and since the solutions lose their radio-activity very rapidly (there is about a 50 per cent reduction in the first hour after the preparation) the likelihood of any radio-activity remaining over during this period and affecting the egg at a later critical moment is remote The amount of radio-activity remaining after twenty-two days, if present at all, should, as determined from physical computation, be infinitesimally small.

The series of intravenous injections again emphasize the specific action of radium emanation in the production of typical areas of subcutaneous extravasations in the developing young, and in addition shows that the placenta may act in the nature of a 'shock absorber' and prevent the embryo from receiving the full effect of the radiation.

We now come to a consideration of the cases wherein pregnant females were treated with external applications of comparatively large doses of gamma-ray radiation. At this time a report is given only for embryos treated towards the end of pregnancy. The writer plans to continue this line of investigation and treat at earlier prenatal periods.

The results emphasize the well-known delayed reaction associated with gamma-ray radiation. There was approximately a ten-day interval following treatment during which no changes were noted in the embryo, and during this period the young animals were born in an apparently normal condition. Acute reactions promptly occurred at the completion of this time, killing half of each litter. The young rats died showing typical radium changes, such as anemia, diffuse edema, and meningeal, spinal-cord, and subcutaneous extravasations. These extravasations were markedly similar to those already described for the series of solution treatments. The liver in these animals showed a fatty degeneration of the hepatic cells similar to the condition reported by Mills (17) after exposing a series of mice to gamma-ray radiation. The only other pathological change noted in these embryos was a desquamation of the lining cells of the intestinal mucosa. This observation is in line with the results emphasized by Hall and Whipple (18) in their experiments on Roentgen-ray intoxication in dogs.

While the animals described above died after showing acute reactions certain of their litter mates (half of the litter) continued to develop apparently normally. This difference in reaction may possibly be due to individual variability or tolerance for the radiation, but it probably can be explained by the fact that certain embryos were slightly farther away from the source of radiation than others, and as the intensity of radiation varies inversely as the square of the distance, even such slight differences in distances that did exist would be sufficient to subject the embryos to a considerable range in intensity of radiation. This is especially important in this case because the source of radiation was only 1 cm. from the body wall of the mother. The quality of radiation, however, remained the same for all the embryos.

It was soon apparent that the animals that lived over the ten-day period had not completely escaped the effect of the radiation, as was shown by a suppression of the full development of the eyes. Eye defects

were noted, such as opaqueness of the pupil, atrophy of the lens, and closing of the lids, which resulted in complete blindness. These animals grew to a normal size, successfully competed with their cage mates for food, and showed absolutely no abnormal neurological condition, except those clearly incident to blindness. At autopsy, in some cases over a year after birth, very decided developmental arrests were noted in the structure of the brain. All grades of such maldevelopment were noted in the condition of the neopallium, from merely a decrease in the size of the hemispheres, which permitted the corpora quadrigemina to be clearly visible from above, to a more marked absence of the cerebral cortex until only a very thin lamina of tissue remained to represent that structure, and there were large areas in the frontal, occipital, and temporal region where no cortex existed at all, so that when the meninges were removed the basal ganglia were clearly seen from without.

This correlation between defects in the development of the eye and the brain has been emphasized by Stockard (19) in his recent paper on developmental rate and structural expression. He states as follows: "The periods of arrest necessary to induce the eye and the brain modifications are so close together or so nearly the same, that one generally finds combinations and mixtures of the defects among the same experimental group of embryos." Again in the same article Stockard has shown that the type of deformity that results from experimental disturbance depends upon the developmental moment at which the interruption occurs. It is significant that the animals of this experiment showed arrests in the development of the neopallial portions of the brain and not in those regions which are ontogenetically older. Apparently the radium emanation, acting towards the end of pregnancy, had affected the development of the brain after the basal ganglia, the cerebellum, and medulla had become fairly well differentiated, and therefore those portions showed no gross changes. But the radium had slowed the developmental rate of the neopallium (which we know is one of the last portions of the brain to differentiate) during its period of active cell proliferation, and that portion of the brain was never able to re-establish its proper rate of development in relation to the other parts of the brain. If the period of treatment had occurred earlier in prenatal existence, other portions of the brain would probably have shown disturbances as well. The writer does not believe that the deformities in the brains of these animals were due to the early production of vascular disturbances later recovered from, but to an actual inhibitory effect of the radiation upon the developing nerve cells. If extravasations had occurred in this group of animals, and were so situated as to affect the development of the cerebral cortex in particular, they probably would have been detected as were even the comparatively small lesions which were associated with the acute reactions. Also, if the effect was largely due to vascular disturbances, from the nature of the radiation employed, one would expect more generalized changes throughout the entire brain. However, on the other hand, Craigie (20), in his recent paper on the relative vascularity of various parts of the central nervous system of the albino rat, suggests that "the vascularization of the more recently evolved centers (of the cortex cerebri) is more susceptible than the more ancient regions to sexual, hereditary or environmental influences."

From a neurological point of view, it is interesting to consider that the animals with practically no cerebral cortex reacted so normally in their ordinary behavior. Except for blindness, there was no other

apparent sensory disturbance, and motor co-ordination appeared perfect. The physiological functions localized in the cerebral cortex of the rat were in these animals apparently transferred to the basal ganglia and other paleokinetic portions of the brain, showing the remarkable degree of compensation possible in the mammalian brain when the disturbing element acts at an early period in its development. In this connection it is worth mentioning that the radium emanation did not produce a sudden traumatic effect, as is normally the case with the experimental production of brain lesions, and in fact, the radium changes were probably prolonged over a considerable period. This condition favored the establishment of compensatory reactions, and exists (as shown by the writer in a recent article (21) even in the case of radium lesions experimentally produced in adult mammalian brains.

The reproductive system completes its development a considerable time after birth, and so it is not at all surprising that these structures should have shown a considerable amount of atrophy due to the developmental arrest during the prenatal period. The ovaries and testes appeared to suffer with equal severity.

An interesting correlative relation was shown by the fact that the other viscera (digestive, excretory, etc.) of the animals that showed marked developmental arrests of the nervous and reproductive systems were apparently normal and the animals grew to an average size. The lungs, liver, kidneys, etc., had differentiated before the physical agent was employed. Further studies with earlier prenatal treatments should throw some light on establishing the critical growth periods of the various embryonic structures.

As a final point, the results of this investigation may be of interest to the clinicians and the laboratory workers who handle large quantities of radium and utilize x-rays. Although the results of this paper deal only with irradiation of the female, there is no reason to believe that the germ cells of the male are more resistant to these destructive agents than those of the female, and, in fact, there is very good experimental evidence to show that spermatozoa of some animals are especially likely to produce abnormal young after exposure to comparatively small quantities of irradiation. Physicians should guard against the possibility of producing developmental arrests such as shown in this article when treating pregnant women, as well as the possibility of altering the human germ cells by irradiation previous to conception.‖

CONCLUSIONS

1. The marked selective action of radium emanation on fast-growing embryonic structures was noted in these experiments.

2. Very decided developmental arrests occurred in the differentiation of the nervous and reproductive systems of mammalian embryos exposed to irradiation towards the end of pregnancy.

3. Experimental animals with greatly reduced, or practically no

‖The writer does not mean to be understood as stating that present-day clinical irradiation treatments produce such effects in the developing young, but it is his personal opinion that such changes are biologically possible. It is not possible to obtain desired information by comparing the amount of exposure that a small mammal can stand with the corresponding dose that a man should tolerate, judging by comparative weights. The small mammal can tolerate very much more radiation in proportion to its weight than a man can.

neopallium, gave apparently normal neurological behavior, except for blindness.

4. Radium emanation, used either in the form of a radio-active solution injected into the adult female, or employed as an external gamma-ray radiation, produced marked areas of extravasation in the subcutaneous connective tissue of the developing young. This suggests that the action of radium emanation might be selective upon the endothelium of blood vessels.

5. Extravasations occurred in the developing young of females treated with radio-active solutions a considerable time before fertilization, and suggest that in some way the faculty of the later developing embryos to form proper blood vascular endothelium had been interfered with.

6. The results so far obtained indicate that gamma-ray radiation is a physical agent admirably adapted to the study of experimentally produced developmental arrests in mammalian embryos.

7. When women are subjected to therapeutic irradiation, especially during the early stages of pregnancy, the clinician should be forewarned concerning the possibility of producing very grave disturbances in the developing child.

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CORRECTION TABLE FOR EMANATION TUBES MEASURED BEFORE EQUILIBRIUM

By MELVIN MOONEY, B. S.

Physicist, Frank E. Simpson Radium Institute, Chicago.

In the routine production of radium emanation tubes for therapeutic uses it is naturally desirable to have the tubes available for use as soon as possible and hence to measure them as soon as possible. The author finds that a tube 2½ hours old is changing in activity slowly enough so that there is no difficulty in getting checks on successive measurements. Of course, if a tube is measured after it has reached transient equilibrium, the value at any later time can be obtained directly by multiplying the original value by $e^{-\lambda_1 t}$ where λ_1 is the decay constant for radium emanation and t is the time elapsed since measuring; but if a tube is measured before it has reached transient equilibrium, then to calculate its value at any later time an additional factor must be used also, this factor depending on how long before equilibrium the tube was measured. The accompanying correction table gives the value of this additional factor as it varies with the time of measuring.

Just how these values were calculated and how the table should be used will be made clear by the accompanying graph (Fig. 1). The

line BCD represents the active deposit of Ra C as a function of the time after the emanation is introduced into the capillary and the tube sealed up. To the right of point C this activity curve falls at the same rate as the decay curve for radium emanation, the tube having reached transient equilibrium at point C. The curve CA is obtained by extrapolating DC backwards according to the same exponential law that applies to CD. Note that the point A is taken where $t = 150$ min., t being the time elapsed since the tube was formed. It is evident that a point on CD corresponding to some other value of t can be obtained from the point A simply by multiplying the activity represented by the latter point by the factor $e^{-\lambda_1 (t-150)}$. The activity at A being taken as unity, the figures in column F_1 of the correction table are the values indicated by points on the curve BC, and the figures in column F_2 are the reciprocals of the corresponding factors F_1. Therefore, if the hard

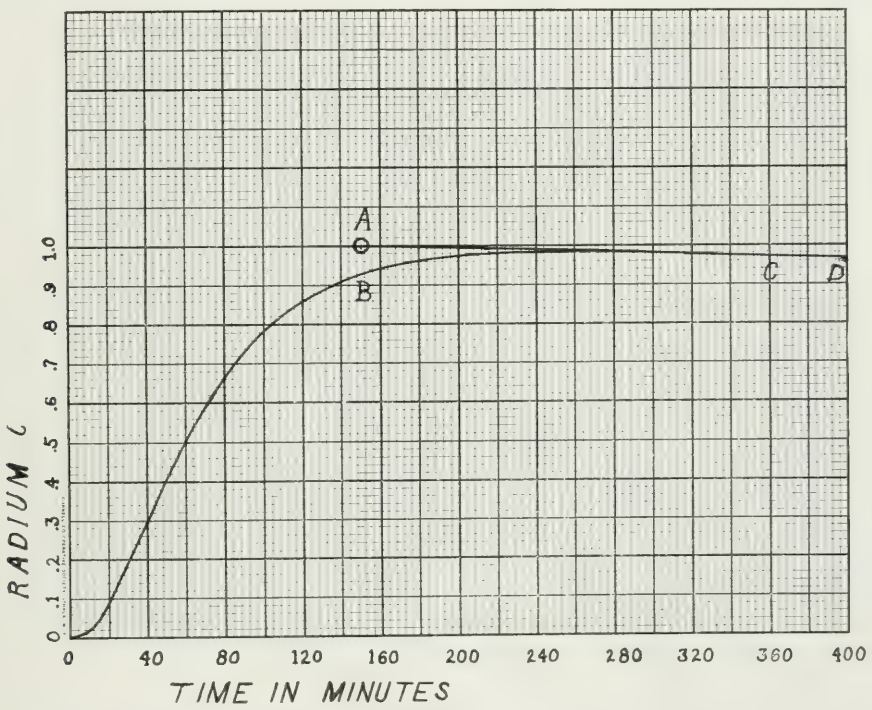

Figure 1.

gamma-ray activity of an emanation tube is measured before transient equilibrium, its activity at any time after equilibrium can be obtained from either of the two equations,

$$a = a_m \frac{e^{-\lambda_1 (t-150)}}{F_1} = a_m F_2 e^{-\lambda_1 (t-150)}$$

where a is the activity at time t, a_m is the activity at the time of measureing, t is the time in minutes since the formation of the tube, λ_1 is the decay constant for radium emanation (1.25×10^{-4}) and F_1 and F_2 are the factors in the correction table corresponding to the time at which the tube was measured.

The calculation of this table is primarily based on the equation[1]

$$N_t = E_o \lambda_1\lambda_2\lambda_3 \left(\frac{e^{-\lambda_1 t}}{(\lambda_2-\lambda_1)(\lambda_3-\lambda_1)(\lambda_4-\lambda_1)} + \frac{e^{-\lambda_2 t}}{(\lambda_1-\lambda_2)(\lambda_3-\lambda_2)(\lambda_4-\lambda_2)} + \frac{e^{-\lambda_3 t}}{(\lambda_1-\lambda_3)(\lambda_2-\lambda_3)(\lambda_4-\lambda_3)} + \frac{e^{-\lambda_4 t}}{(\lambda_1-\lambda_4)(\lambda_2-\lambda_4)(\lambda_3-\lambda_4)} \right)$$

where N_t is the number of atoms of RaC present at the time t, E_o is the number of atoms of radium emanation present when the tube was formed, t is the time in minutes since the tube was formed and λ_1, λ_2, λ_3 and λ_4 are the decay constants for radium emanation, Ra A and Ra B and Ra C respectively. Then on the assumption that a tube reaches transient equilibrium in 360 minutes, the factors F_1 and F_2 for a given time t are obtained from the equations

$$F_1 = \frac{1}{F_2} = \frac{N_t\, e^{-\lambda_1 (360-150)}}{N_{360}}$$

($N_{360} = N_t$ for the value $t = 360$.) The values of λ_1, λ_2, λ_3 and λ_4 used were those corresponding to the half-value periods 3.85 days, 3, 26.8 and 19.5 min. respectively.* Calculations of F_1 and F_2 were made with a seven-place table of logarithms for the values of t at 5 min. intervals from 150 to 200 min., at 10 min. intervals from 200 to 240 min. and at 20 min. intervals from 240 to 300 min. Intermediate values for F_2 were obtained by interpolation, the second order differences between adjacent values being made practically constant within the interval between two calculated values of F_2. The intermediate values of F_1 were obtained from the corresponding values of F_2 by means of a slide rule.

In making use of this correction table there are two precautions which should be observed: (1) The table takes account of Ra C only, so the tubes should be measured through sufficient screening (2 cm. of lead) practically to eliminate all but the hard gamma-rays of RaC. (2) If the day's emanation is to be used, not in one tube, but in several the capillary should be split into the smaller tubes as soon as possible after the emanation is forced into the capillary. Otherwise, if time is allowed for an appreciable active deposit to form, the active deposit and the emanation are not likely to be distributed proportionately among the smaller tubes when the capillary is subdivided.

It may be worth pointing out that the use of this table facilitates the calculation of the efficiency of pumping. If the emanation is pumped each day at the same hour and if loss due to decay while pumping is neglected, the yield per gram of radium should be 164.7 millicuries of emanation. At the end of 150 min. this amount has decayed to $164.7 \times e^{-150\lambda_1}$ millicuries. But in order to get the theoretical activity corresponding to the point A it is further necessary to multiply by the factor

[1]Rutherford, Radioactive Substances and Their Transformations, p. 422.

*These are the values which Rutherford states were used by Moseley and Makower in calculating a table, somewhat similar to the one printed with this article, which is printed in Rutherford's book, p. 499. But there is a discrepancy between Moseley and Makower's table and my own, the maximum difference between the two being about .06% at t = 150. However, Moseley and Makower's table is also given in Makower and Geiger's book, Practical Measurements in Radio-activity; and there it is stated that in calculating the table the half-value period for Ra B was taken to be 26.7 min. It seems quite likely, then, that the discrepancy between the two tables is due to a difference between the values assumed for the decay constant of Ra B.—M. M.

1.0089 to account for the difference between secular and transient equilibrium. We thus get 163.0 millicuries per day per gram of radium as the 100% yield, after the measured values of the tubes have been corrected according to the table.

If the choice of $t_A = 150$ as the time at which the value on curve AC is taken as unity is not convenient, it is quite apparent without further explanation how to obtain a similar table for any other value of t_A which may be desired; the table may be used as printed if the value of the standard used is multiplied by the factor $e^{-\lambda_1 (t_A - 150)}$.

CORRECTION TABLE

t	F_1	F_2	t	F_1	F_2
150	.9292	1.0763	192	.9694	1.0316
151	.9307	1.0745	193	.9699	1.0311
152	.9322	1.0727	194	.9704	1.0306
153	.9337	1.0710	195	.9708	1.0301
154	.9351	1.0694	196	.9713	1.0296
155	.9365	1.0678	197	.9717	1.0291
156	.9378	1.0662	198	.9721	1.0286
157	.9392	1.0647	199	.9726	1.0282
158	.9405	1.0632	200	.9730	1.0278
159	.9418	1.0618	202	.9737	1.0270
160	.9430	1.0604	204	.9744	1.0262
161	.9442	1.0591	206	.9751	1.0255
162	.9454	1.0577	208	.9758	1.0248
163	.9465	1.0565	210	.9764	1.0242
164	.9477	1.0552	212	.9770	1.0236
165	.9488	1.0540	214	.9775	1.0231
166	.9499	1.0528	216	.9780	1.0226
167	.9509	1.0517	218	.9784	1.0221
168	.9519	1.0506	220	.9788	1.0217
169	.9528	1.0495	222	.9792	1.0213
170	.9538	1.0484	224	.9795	1.0209
171	.9547	1.0474	226	.9798	1.0206
172	.9556	1.0464	228	.9801	1.0203
173	.9565	1.0455	230	.9804	1.0200
174	.9574	1.0445	232	.9806	1.0198
175	.9582	1.0436	234	.9808	1.0195
176	.9590	1.0427	236	.9810	1.0193
177	.9598	1.0419	238	.9812	1.0191
178	.9606	1.0410	240	.9814	1.0190
179	.9613	1.0402	245	.9816	1.0187
180	.9621	1.0394	250	.9818	1.0185
181	.9628	1.0387	255	.9819	1.0184
182	.9635	1.0379	260	.9820	1.0183
183	.9641	1.0372	265	.9819	1.0184
184	.9647	1.0365	270	.9818	1.0185
185	.9654	1.0358	275	.9816	1.0187
186	.9660	1.0352	280	.9814	1.0189
187	.9667	1.0345	285	.9811	1.0192
188	.9673	1.0339	290	.9808	1.0196
189	.9678	1.0333	295	.9805	1.0199
190	.9683	1.0327	300	.9801	1.0203
191	.9689	1.0322			

UNUSUAL CASE OF MULTIPLE MYOMATA OF THE UTERUS.

By Acheson Stewart, M.D., and William H. Cameron, M.D.,
Pittsburgh, Pa.

On November 7th, 1921, Miss M. W., age 41 years (single) was admitted to the surgical service of Dr. Stewart at the Western Pennsylvania Hospital. The following history was noted: Six years ago patient first noticed a small growth in lower abdomen. This growth gradually increased in size. Patient menstruated regularly every 28 days, periods lasting 4 to 6 days. During the past two years has had considerable pain with increased flow. More recently has had more or less continuous hemorrhage. During the past year patient has been unable to work.

Examination: Uterus enlarged and extending to umbilicus. It is fixed and irregular in outline. Little tenderness noted on manipulation. Profuse hemorrhage. Patient's general condition grave, has valvular heart lesion and profound anaemia. Patient not in condition for operation. Decided to use radium for hemorrhage control.

On November 9th, 1921, 50-milligrams of radium element, screened with 0.5 mm. silver, 1.0 mm. brass and 3.0 mm. rubber was introduced in uterus for six hours. This treatment was completed on November 10th.

On November 15th hemorrhage was under control and on November 21st uterus seemed to be slightly reduced in size.

Because of the progress made it was decided to continue radium applications and on November 21st, 27th and 28th, 50-milligrams was again applied, the radium being screened as above noted.

On December 1st the blood count was as follows: R. B. C. 4,420,000; W. B. C. 6200 and haemo, 65%. The improvement in general condition was striking and the decrease in size of the uterus noticeable. On this date the patient was sent home.

On January 4th, 1922, patient returned for observation. Uterus found to be greatly reduced in size, was freely moveable and no hemorrhage had been noted since November 15th. Patient hesitated to undergo operation and requested further radium applications. On January 4th 50-milligrams was placed for 24 hours and on January 7th 25-milligrams for six hours. Patient was again sent home to be re-admitted on February 10th. At this time progressive improvement was noted and an application of 50-milligrams for 24 hours used. Patient was again sent home.

On March 5th the patient was suddenly seized with violent pain in lower abdomen, resembling in every particular typical labor pains. In telephone communication with the patient's physician, Dr. Stewart, made a provisional diagnosis of detached myoma in uterine cavity and ordered patient to hospital for operation. On entering hospital the general condition of patient was found to be good. Haemo. 70%, temperature 102.6, pulse 120 to 130, respiration normal. The pain was so severe, however, that it required an injection of ½ grain morphine to control.

On March 6th the patient was prepared for operation, it being the intention to empty the cavity by curetting. On examination under anesthetic, it was found that the canal was completely blocked by the mass in the lower uterine segment, consequently a complete hysterectomy was done, the operation being accomplished without incident.

The pathological report was as follows: Uterus weighed 1,025 gm. It is large and not unlike a gravid uterus. It measures 15 cm. in diameter. On opening, an irregularly distended cavity is seen. There is one mass 15 cm. in diameter. It is covered by endometrium which is hemorrhagic. There is a free nodule (6 cm. in diameter)in the uterine cavity. It is necrotic and hemorrhagic and there is no evidence to show its previous point of attachment. The uterine wall averages 3.5 cm., and scattered in it are numerous nodules 2 to 4 cm. These nodules, on coarse section, show typical tendinous white tissues and there are no signs of degeneration.

Remarks: The severe pain is accounted for in the effort of the uterus to empty itself of the free myoma and the impossibility of this being spontaneously accomplished by reason of the blocking of the canal by the larger mass in the lower uterine segment. It is difficult, however, to account for the detached mass, especially as no evidence of any previous attachment to uterine wall was found. It may be that the radiations were accountable for the absorption of possible small pedicles. The subsequent degeneration in the mass from lack of blood supply would indicate this. The hemorrhagic condition of the endometrium covering the larger mass is accounted for by the pressure produced by the small mass in its efforts to pass through the canal.

This case demonstrates several important points in radium applications. First, its utility in stopping severe hemorrhage; second, that repeated applications of a reasonable amount of radium will not materially interfere with a subsequent operation; third, its utility in cases of large fibroids wherein operation on account of general condition of patient, is contra-indicated; fourth, it again brings out the point that pedunculated fibroids, when there can be diagnosis and operation, are surgical cases only; fifth, that in cases radiated only and in which sudden pain develops some months later, operation, looking towards rapid emptying of uterus should be considered; and sixth, complete hysterectomy is to be preferred to other measures to accomplish this end, provided, of course, that the patient's general condition permits. It is to be regretted that this unusual specimen, including tubes and ovaries, was not sectioned to note minute effect of radiation on the involved tissue.

AMERICAN RADIUM SOCIETY

On Monday and Tuesday, May 22 and 23, 1922, the American Radium Society held its seventh annual meeting at the Planters Hotel, St. Louis, Missouri, under the presidency of Doctor George E. Pfahler of Philadelphia. The following scientific papers were presented in the session on Monday:

Lymphosarcoma and other Glandular Enlargements of the Neck; Their Radiation Treatment. Edward H. Skinner, M.D., Kansas City.

Experience with Radium in the Treatment of Bone Tumors. Joseph C. Bloodgood, M.D., Baltimore.

Treatment of Carcinoma of the Esophagus by Radiation. Walter Mills, M.D., and John Kimbrough, M.D., St. Louis.

Statistics and Technic in the Treatment of Carcinoma of the Rectum by Radiation. Harry H. Bowing, M.D., Rochester, Minn.

Technic and Ante-Operative Radiation for Carcinoma of the Breast. Russell H. Boggs, M.D., Pittsburgh.

Statistics and Technic in the Treatment of Carcinoma of the Breast by Radiation, from the Standpoint of the Surgeon. Burton J. Lee, M.D., New York.

Statistics and Technic in the Treatment of Carcinoma of the Uterus and Pelvis with the Combined Use of Radium and X-Rays. Henry Schmitz, M.D., Chicago.

Statistics and Technic in the Treatment of Malignant Disease of the Uterus and Pelvis by Moderate Quantities of Radium. John G. Clark, M.D., Philadelphia.

Results of Treatment of Carcinoma of the Cervix, with Statistics and Technic. Curtis F. Burnam, M.D., Baltimore.

Statistics and Technic in the Treatment of Certain Benign Uterine Conditions by Radium. Leda J. Stacy, M.D., Rochester, Minn.

Statistics and Technic in the Treatment of Uterine Fibroids by Radiation. James A. Corscaden, M.D., New York.

Carcinoma of the Uterus, with Pregnancy, Treated Successfully by Radium, with Delivery of Normal Child. C. Everett Field, M.D., New York City.

Radium Therapy in Cancer of the Prostate. Hermon C. Bumpus, M.D., Rochester, Minn.

Statistics and Technic in the Treatment of Carcinoma of the Bladder by Radiation. Benjamin S. Barringer, M.D., New York.

On Monday evening the annual dinner was held at the Planters Hotel, after which Dr. Pfahler made the president's annual address, on Protection in Radiology. On Tuesday the following scientific papers were presented:

Statistics of the Intra-Oral Group of Carcinomas. Douglas Quick, M.D., New York. (Read by title).

The Treatment of Infected Tonsils by Radium. C. Augustus Simpson, M.D., Washington. In the absence of Dr. Simpson, Dr. Carl F. Robinson of Barre, Vt., who was to open the discussion of this paper, presented a very interesting discussion of his treatment with radium in 75 cases of infected tonsils.

Radium Treatment of Nasal Polyps. H. R. Lyons, M.D., Rochester, Minn.

Statistics and Technic in the Treatment of Malignant Disease of the Antrum by Radium. D. Crosby Greene, M.D., Boston.

Statistics and Technic in the Treatment of Malignant Neoplasms of the Larynx. Douglas Quick, M.D., New York. In the absence of the author this paper was read by Dr. William S. Stone of New York.

Technic in the Application of Radium Needles. William L. Clark, M.D., Philadelphia.

Statistics and Technic in the Treatment of Malignant Disease of the Skin by Radiation. Frank E. Simpson, M.D., Chicago. (Read by title).

Statistics and Technic in the Treatment of Malignancy of the Skin by Radiation. Howard Morrow, M.D., and Lawrence R. Taussig, M.D., San Francisco.

The Treatment of Superficial Cancer, with Statistics and Technic. D. T. Quigley, M.D., Omaha.

Comparative Measurements Between Radium and X-Rays Concerning Energy Absorbed at Depth. Harvey R. Gaylord, M.D., and Dr. Carl W. Stenstrom, Buffalo.

On Ionization Measurements. Gioacchino Failla, E. E., New York.

Proposed Collective Investigations of Certain Aspects of the Treatment of Malignant Disease. Robert B. Greenough, M.D., Boston.

The Present Field for the Use of Radium and the X-Ray in the Treatment of Malignant Neoplastic Disease. William S. Stone, M.D., New York.

The Biological Effects of Radio-Active Substances and X-Rays on Cell and Tissue Structures. Leo Loeb, M.D., St. Louis, Mo.

Two Important Points Regarding Cancer Immunity from the Radium Therapist's Standpoint. Carroll Chase, M.D., New York.

Following the scientific papers there was a brief demonstration of apparatus, applicators and technique.

The meetings were well attended, and it was the consensus of opinion that the session was the most successful which the society has held.

For the ensuing year the following officers were elected: President, Dr. R. E. Loucks, Detroit, Mich.; President-elect, Dr. James T. Case, Battle Creek, Mich.; First Vice-President, Dr. William S. Newcomet, Philadelphia, Pa.; Second Vice-President, Dr. H. H. Bowing, Rochester, Minn.; Secretary, Dr. Edwin C. Ernst, St. Louis, Mo.; Treasurer, Dr. Douglas Quick, New York, N. Y.

REVIEWS AND ABSTRACTS

Radium Therapy, by Dr. Frank Edward Simpson. The work contains 391 pages, with 166 original illustrations. C. V. Mosby Co., St. Louis, Mo., 1922. $7.00 net.

Dr. Simpson is prominently identified with the development of radium therapy in the United States, and is doing the largest work in this field in Chicago, where he is the director of the Frank Edward Simpson Radium Institute. Out of his rich experience in this field Dr.

Simpson has drawn the material for an American work which summarizes the important developments in this field in which America has now taken the lead. The book is written strictly from the standpoint of radiumtherapy, and for this reason is far more valuable to those who wish specific information in this work than are the texts which consider radium as essentially an alternative to the x-ray.

The work includes twenty-one chapters and a comprehensive bibliography containing references to about 1900 articles. All who are working in radiumtherapy today in the present knowledge of this branch of science must be students, and these will find Dr. Simpson's book a most valuable addition to the too few books which may be considered authoritative. To the general practitioner the book will be of great value in helping him to gauge more accurately the value and limitations of radium therapy.

Below are given the chapter headings from this book:

1. The Radioactive Substances.
2. Radium—Its Origin and Chemical Nature.
3. Radium Emanation and Radioactive Deposit.
4. The Technic of the Preparation of Radium Emanation for Therapeutic Use and the Method of Measuring Its Gamma Ray Activity.
5. The Radiations from Radium and Its Decay Products.
6. Absorption and Filtration of Rays.
7. The Absorption of Gamma Rays in Water.
8. Physical and Chemical Effects of Radium Rays.
9. Biologic Effects of Radium Rays.
10. Biologic Effects of Radium Rays (Continued).
11. The Radium Reaction.
12. Therapeutic Apparatus.
13. Dosage.
14. The Technic of Radiation.
15. Radium in General Surgery.
16. Radium in Gynecology.
17. Radium in Dermatology.
18. Radium in Ophthalmology, Otology, Rhinology and Laryngology.
19. Radium in Diseases of the Ductless Glands.
20. Radium in Internal Medicine.
21. Professional Injuries Due to Radium.

Bibliography.

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The Principles of Physics and Biology of Radiation Therapy by Dr. Bernard Kroenig and Dr. Walter Friedrich of the University of Freiburg in Breisgau, translated by Dr. Henry Schmitz, with an appendix containing articles by several of Dr. Friedrich's assistants, including one by the translator. The work contains 271 pages with 86 textual figures and 20 colored and 11 black and white plates, and 32 tables. Rebman Company, New York, 1922. $8.00 net.

Those who know of this interesting and important work of Kroenig and Friedrich, which appeared in 1918, will welcome Dr. Schmitz' admirable translation. For the benefit of those who have not heard of this work we reproduce a synopsis of the chapter headings below. A reading of these makes clear the importance of this book. One of the articles in the appendix contains data on the isodoses of short radium

tubes obtained by Dr. Schmitz, working in Friedrich's laboratory, and extends the work of Kroenig and Friedrich, in a very useful way. This is one of the outstanding works in radiotherapy and should find a prominent place among the books, which are stimulating and useful to the radiotherapist, whether his interest is in radium, x-rays, or both.

Part I. The Physical Principles of Radiation Therapy, 1—Definitions, 3—Measuring of Intensity, Hardness and Dose, 8—Importance of Secondary Radiation for the Dose, 77.

Part II. The Biologic Principles of Radiation Therapy, 102—Investigations on the Relation of Intensity of the Biologic Action to the Hardness of the Rays in Frog Larvae, 117—Investigations on the Relation of the Hardness of the Ray to the Intensity of the Biologic Action in Human Tissue, 131—The Significance of the Dosimeter in the Determination of the Biologic Factor, 146—Investigations on the Relation of the Intensity of Rays of Like Doses on the Intensity of the Biologic Action, 158—Biologic Observations on the Law of Intermittent Dosage, 167—Biologic Observations of the Influence of Factors like Diathermy, Heat and Secondary Radiations on the Intensities of the Biologic Action of X- and Gamma-rays, 171—Dependence of the Biologic Action on the Kind of Tissue. Sensitiveness Quotient, 195—On the Relation of the Individual to the Intensity of the Biologic Action with Like Doses, 201.

Appendix, 209—Experimental Investigations of the Influence which the Focus Skin Distance and the Size of the Field have on the Quotient of the Dose, 209—Experimental Contribution to the Question of Secondary Ray Therapy, 225—The Distribution of the Radiation Dose in Intracorporeal Radium and Mesothorium Therapy, 241—The Determinations of Equal Intensity Curves (Isodoses) of Short Radium Capsules, 255—The Importance of Filtration on the Dose in Intracorporeal Applications of Radium and Mesothorium, 264—Index, 269.

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Medical Uses of Radium. Studies of the Effects of Gamma Rays from a Large Quantity of Radium by various authors. Medical Research Council, London. Published by His Majesty's Stationery Office, 1922. Special Report Series No. 62. Price 5s. net.

"In 1919 the ministry of munitions, recognizing the assistance which the (then) Medical Research Committee had brought to the Ministry in various directions during the war, offered to deposit with the committee for the purposes of medical research nearly 5 grammes of hydrated radium bromide—or about 2½ grammes of radium element, during the period between its collection from innumerable gun-sights, watch-dials and other instruments of war, and its final disposal for other purposes. This offer was gratefully accepted, and the whole quantity of radium salt thus made available for research work was, in the first instance, put into the charge of the late Mr. Cecil R. C. Lyster, Professor W. S. Lazarus-Barlow, and Professor Sidney Russ, who, by kind permission of the authorities at the Middlesex Hospital, accepted the responsibility for its safe custody under safeguards approved by the ministry and the committee.

"The immediate object of the inquiries thus begun was to determine the curative value in malignant disease of penetrating radiation of extremely short wave-length, like that of the gamma rays of radium, with a special view to ascertaining whether the use of this very large

amount of radium would give appreciably different results, whether in kind or degree, than had been obtained hitherto with quantities of about a tenth of the amount. The work was done in the cancer wards and research laboratories of the Middlesex Hospital, by courtesy of the Weekly Board, and with the clinical collaboration of the physicians and surgeons. When the radium salt was not in actual use for the treatment of patients, it was employed for the experimental exposure of various animals, and for this side of the work a wholetime research grant was made to Dr. Helen Chambers.

"The chief results of this phase of the work are given in the present report. It contains accounts of the methods employed, of the results of treatment of malignant disease, and of the histological examination of irradiated tissues obtained both from human cases and from animals."

"At the conclusion of the preliminary period of mass experiment at the Middlesex Hospital, the council arranged for the distribution of the radium salt among several research centers with a view to an extended and co-ordinated inquiry. The allocation was completed during 1921, and at nearly every selected center work is already actively in progress. These centers are at present the following: In London, the Middlesex Hospital, University College Hospital, King's College Hospital, St. Bartholomew's Hospital, the London Hospital and the Radium Institute; in the provinces, the General Hospital, Birmingham; in Wales, the King Edward VII Hospital, Cardiff; and in Scotland, the Royal Infirmary, Aberdeen. The Irish Public Health Council in Dublin, also, were entrusted with a fraction of the salt in 1920, and have organized a local scheme of research.

The articles included in this book are the following:

1. On the Use of the Gamma Rays from a Large Quantity of Radium in the Treatment of Malignant Disease. Part 1 by S. Russ, D.Sc. Part 2 by W. S. Lazarus-Barlow, M.D., F.R.C.P., S. Russ, D.Sc., and Helen Chambers, M.D.

2. On the Histological Changes produced in certain Neoplastic and Normal Tissues in Man by the Gamma Rays of Radium. By W. S. Lazarus-Barlow, M.D., F.R.C.P.

3. On the Histogical and some other Changes Produced in Animals by Exposure to the Gamma Rays of Radium. By W. S. Lazarus-Barlow, M.D., F.R.C.P.

4. Histological Examination of the Brains of Animals Exposed to the Gamma Rays of Radium. By T. Morowoka, M.D., and F. W. Mott, M.D., F.R.S.

5. Observations on the Effects Produced on the Bone-Marrow by Exposing Rabbits to 5 Grammes of Radium Bromide. By C. Price-Jones, M.B.

6. On the Average Range of Beta Rays in Different Metals. By G. A. Sutherland, M.A., and L. H. Clark, B.Sc.

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Harold O. Jones, M.D. (Chicago). Report of Cases Treated with Radium in the Gynecological Service at St. Luke's Hospital. Surgery, Gynecology and Obstetrics, xxxiii, 409-412, Oct. 1921.

"This report covers a study of over 500 patients treated with radium by Dr. Watkins, Dr. Curtis and myself."

"1. Fibroids—120 Cases—Because the dividing line between these

cases and those considered in the hæmorrhage group is not always definite—the principal symptom in each being bleeding—only patients with definitely palpable uterine fibroids are here considered."

"The technique followed is surgical aseptic preparation with careful iodinization of the vagina and cervical canal; dilation of the cervix; diagnostic curettage with careful microscopic study of the scrapings; insertion of the radium capsule well up into the uterine cavity; packing the vagina with rubber dam or glove to hold the rectum and bladder away from the uterus."

"The dosage has varied from 1,000 to 1,800 millicurie hours. Recently we have been using a smaller dose in some cases with ½ millimeter gold screen, but the majority of these cases have been treated with the larger dose, with the radium screened with two capsules each ½ millimeter in thickness."

"The postoperative course of patients treated with radium in this manner is about the same as that following any curettage, except that the serous discharge is usually more profuse and persists for a longer period of time. The menstrual reaction after radium varies with individuals; some do not have any periods after treatment, while others have as many as three, usually decreasing in amount."

"It has been necessary to repeat the radium in 7 cases, after second treatment cure has been obtained for a period from 6 months to 1 year. Of all cases treated we now know that 69.1 per cent have been entirely relieved of symptoms for over 2 years. Not enough time has elapsed since the treatment of 22.1 per cent of cases to classify them otherwise than as improved. From 8.8 per cent no recent report has been received."

"2. Hæmorrhage—129 Cases—In no other division of radium treatment is it so necessary to take into consideration so many different factors in the regulation of the dosage as in the patients still in the active child-bearing age who are suffering from so-called idiopathic hæmorrhage. Radium insertion should not be resorted to in these cases until organotherapy has been given a thorough trial."

"The dose that in one patient produces only a reduction of the periods to normal or a temporary amenorrhœa, might possibly produce a permanent menopause in a patient with less radium tolerance; while on the other hand a very small dose may only increase the flow, meaning in the one an insufficient radiation but in the other a prodrome of the menopause. Careful observation of the blood pressure and tabulation of the nervous symptoms are valuable aids in the diagnosis of the approaching menopause. From 750 to 1,000 millicurie hours is the maximum dose for the average individual. However, it is considered better to give initial doses of about 250 millicurie hours and repeat after three or more months if necessary, rather than to produce a period of amenorrhœa."

"In the bleeding of the menopause radium is practically specific, one treatment of 1000 millicurie hours with 2 millimeter gold screen or about 600 millicurie hours with single screen, being sufficient in most cases to bring on the permanent menopause. The symptoms are here also somewhat more acute but fairly easily controlled. The first menstrual period is often profuse, the second less, and rarely does the third amount to more than a spotting."

"Eighty-one per cent of cases have remained relieved of symptoms over 2 years; 16 per cent have been relieved of their symptoms but not

sufficient time has elapsed to be sure of cure. From 3 per cent no recent report has been received."

"3. Carcinoma—100 Cases.

"The technique varies but little from that described before except that the radium inserted into the uterus is doubly screened for distant radiation of the tissues of the broad ligaments. Also needles containing radium are inserted directly into the tumor tissue using the tissue to screen the adjacent structures. In the same way radium emanations may be buried in the malignant growth and left until their full value is used. Additional capsules of radium are placed against the cervix held in place by rubber dam which also holds away the rectum and bladder."

"The dosage for carcinoma is about 3,500 millicurie hours for the initial treatment with a reduction in the amount for the following doses. The number of treatments vary with conditions found after about 8 to 12 weeks as well as the tolerance of the patient to radium and complications which may have arisen."

"The consideration of the treatment of carcinoma would be incomplete without urging the use of the x-ray. Exposures of 30 to 50 minutes to heavily screened rays with a voltage of 140,000 volts over the entire area are beneficial."

"There were 35 per cent of the cases of carcinoma of the uterus diagnosed inoperable in which radium was used as a palliative agent, and in all it was of benefit."

"In 45 per cent radium was used combined with operation either given before operation, following it, or both before and after operation. In addition most of the cases have had series of x-rays."

"Many of the cases treated over the 5 year limit have been those sent from out of the city and letters have failed to reach any one who could give us the details of her progress after our last report. Five cases have remained free from definite recurrence for a period from 1½ to 2 years; one case for over 3 years. The remainder have not been treated long enough to render any other report than that recovery is doubtful."

"4. Leucorrhœa—60 Cases—Dr. Curtis has been especially interested in the intensive study of chronic leucorrhœa. A brief summary of this work and its continuation is given below."

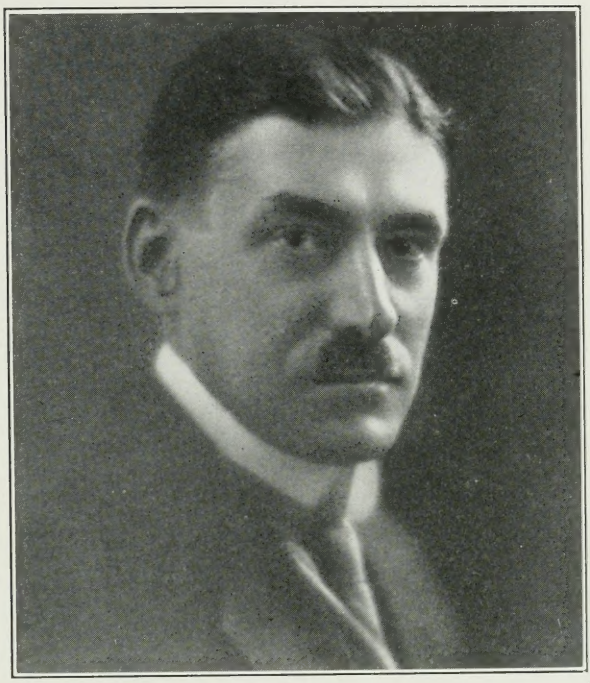
"The technique varies slightly from that described before. At the time of cervical dilatation careful observation of the presence of cervical strictures and granulations is made. Two 25 milligram radium capsules, ½ millimeter gold screen, and covered with rubber tissue are sutured in the cervix for about 6 hours."

"At the time of operation infected Skene's ducts are slit open and fulgurated; infected peri-urethral glands are destroyed as are the Bartholin ducts if they harbor infection."

"Thirty-six of the cases are now cured; 11 are improving; 10, not having been treated sufficiently and not enough time elapsing, are classified as doubtful; 3 cases have not only been cured of their discharge but have since become pregnant. Four patients have at present symptoms of an approaching menopause."

"5. Miscellaneous—100 Cases—These cases run the pathological gamut from superficial skin lesions to inoperable carcinoma of the bowel, including various benign and malignant tumors not within the scope of this report."

OBITUARY



RUSSELL HERBERT BOGGS, M. D.

On Friday morning, June 2, 1922, Doctor Russell H. Boggs died of heart failure at his home in Pittsburgh, following a brief illness.

Dr. Boggs was born at Evans City, Pennsylvania, December 11, 1873, his parents being J. Walton Boggs and Sarah E. Johnston Boggs. The family is one of the oldest and best known in Western Pennsylvania, having first settled there in 1763. Dr. Boggs is survived by his mother and his wife, Mrs. Etta A. Houck Boggs. His first wife, who was Miss Blanche S. McCready, died in 1910.

After attendance in the public schools in Allegheny and the Pittsburgh Academy, he graduated in medicine from the medical department of the Western University of Pennsylvania in 1897. Following a brief period of general practice in Allegheny, he went abroad where he studied at the St. Louis Hospital in Paris, and at the University of Vienna. In Vienna he first became interested in the use of the x-ray and following a postgraduate course at the Skin and Cancer Hospital in New York, Dr. Boggs returned in 1900 to Pittsburgh and began the practice of roentgenology in Allegheny. Several years later he moved his office

to the Empire Building in Pittsburgh where he was located until his death.

The pioneer in Pittsburgh to make a specialty of roentgenology, Dr. Boggs was a charter member of the American Roentgen Ray Society, which owes much to his energy and enthusiasm, for he was a constant attendant at the society's meetings and a regular contributor to the programs.

Dr. Boggs was formerly radiographer at the Allegheny General Hospital and professor of radiography and phototherapy in the Western Pennsylvania Medical College and the Pittsburgh Dental College. He was roentgenologist at the St. Francis Hospital, Columbia Hospital, Pittsburgh Hospital and he was consulting roentgenologist to the Mercy Hospital. These appointments he later gradually resigned, retaining only an active connection with the Pittsburgh Hospital. He was a member of the American Medical Association, the Pennsylvania State Medical Society, Allegheny County Medical Society, American Roentgen Ray Society, Pittsburgh Academy of Medicine, American College of Physicians, The Radiological Society of North America, the New York Roentgen Ray Society, Roentgen Ray Society of Central Pennsylvania, American Radium Society. During the war Dr. Boggs served as a Lieutenant in the United States Navy.

Dr. Boggs was one of the outstanding radiotherapists in America; a tireless worker, a deep student and a prolific writer. His work with the x-ray early trended from the diagnostic to the therapeutic field and when, about a decade ago, the radioactive substances began to assume importance in therapy, Dr. Boggs was the first in Pittsburgh to take up their use. At the time of his death Dr. Boggs' practice in radium and x-ray therapy was the largest in Pittsburgh, and the results by the methods which he employed,—many of which were very daring and original,—were among the best which have been secured anywhere in the world. His unbounded enthusiasm in the face of discouraging obstacles, his cordiality in assisting younger men, and his constant faith and optimistic outlook on the problems which came to him, were conspicuous points in Dr. Boggs' character.

In the passing of Dr. Boggs, radiotherapeutics loses one of its most brilliant exponents, and a host of friends sincerely mourn the loss of a loyal companion and generous counselor. Dr. Boggs' death leaves a vacancy which will be impossible to fill, but his profession will be richer, greater and better because of his having lived and wrought with all the ardor of his great and loving soul.

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